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NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM

SECOND ANNUAL REPORT OF THE DIRECTOR OF THE NATIONAL HEART AND LUNG INSTITUTE

MARCH 10, 1975

SECOND ANNUAL REPORT OF THE DIRECTOR OF THE NATIONAL HEART AND LUNG INSTITUTE

SUBMITTED TO
THE PRESIDENT OF THE UNITED STATES
FOR TRANSMITTAL TO
THE CONGRESS OF THE UNITED STATES
IN ACCORDANCE WITH PUBLIC LAW 92-423

MARCH 10, 1975

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health
National Heart and Lung Institute
DHEW Publication No. (NIH) 75-748

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL HEART AND LUNG INSTITUTE

March 10, 1975

The President
The White House
Washington, D.C.

Dear Mr. President:

I am pleased to submit to you for transmittal to the Congress the Second Annual Report on the National Heart, Blood Vessel, Lung, and Blood Program. This report has been prepared in accordance with Section 413(b) of the Public Health Service Act, as amended by the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423, 86 STAT 679).

As required by the Act, we have reported on progress in the Program during calendar year 1974 and presented a revised and updated five-year plan for the Program. The resource projections discussed in the Report are based on scientific and professional judgement as to the resources required to accomplish program objectives within the time frame indicated. However, it is recognized that the allocation of national resources to execute the Program must be determined in relationship to other national needs at any given time.

Respectfully,

Robert L. Ringler

Robert L. Ringler, Ph.D.
Acting Director

ABBREVIATIONS

AEC - Atomic Energy Commission

DHEW - Department of Health, Education, and Welfare

ERDA - Energy Research and Development Administration

FDA - Food and Drug Administration

IATC - Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources

NASA - National Aeronautics and Space Administration

NHLI - National Heart and Lung Institute

NIAMDD - National Institute of Arthritis, Metabolism, and Digestive Diseases

NIH - National Institutes of Health

PSRO - Professional Standards Review Organization

U.S. - United States

USDA - U.S. Department of Agriculture

U.S.S.R. - Union of Soviet Socialist Republics

VA - Veterans Administration

ADP - Adenosine Diphosphate

AMIS - Aspirin Myocardial Infarction Study

CAST - Coronary Artery Surgery Trial

CCU - Coronary care unit

CDP - Coronary Drug Project

CF - Cystic fibrosis

COPD - Chronic obstructive pulmonary disease

ECG - Electrocardiogram

G6PD - Glucose-6-phosphate dehydrogenase

Hb A - Normal adult hemoglobin

Hb F - Fetal hemoglobin

Hb S - Sickle cell hemoglobin

Hb S-C disease - Genetic variant of sickle cell disease

Hb S-thalassemia - Genetic variant of sickle cell disease

HDFP - Hypertension Detection and Follow-Up Program

LRC - Lipid Research Clinic

L/S - Lecithin-to-sphingomyelin ratio

MRFIT - Multiple Risk Factor Intervention Trial

mRNA - Messenger ribonucleic acid

NHBPEP - National High Blood Pressure Education Program

pCO_2 - Partial pressure of carbon dioxide

pO_2 - Partial pressure of oxygen

RDS - Respiratory distress syndrome

SCORs - Specialized Centers of Research

TDI - Toluene di-isocyanate

S/S disease - Sickle cell anemia

I. INTRODUCTION

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This is the second annual report on the National Heart, Blood Vessel, Lung, and Blood Program, submitted to the President for transmittal to the Congress.

This Program is of great importance to the American people. It has potential value for every citizen in our country. It deals with diseases that affect all age groups, both men and women, all ethnic groups, and all strata of society. These diseases have a profound impact on our nation's health and economy. More than 30 million Americans suffer from these diseases, the annual economic costs are in excess of $40 billion, and heart and blood vessel diseases alone are responsible for more deaths than all other causes combined (see Figure 1). However, for the first time in a quarter of a century, deaths from the number one killer--coronary heart disease--have shown a slight decline, resulting in saving approximately 14,000 Americans a year. Deaths from stroke, hypertension, and rheumatic heart disease are continuing their downward trend, and the death rate from emphysema and chronic bronchitis, after years of sharp increases, has leveled off.

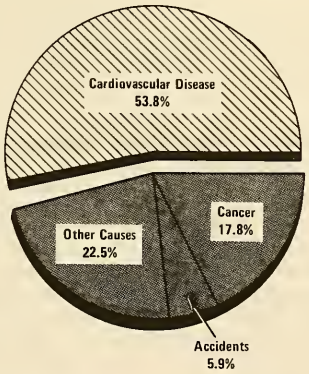


Figure 1. Deaths from all Causes, United States, 1973

Fortunately, through scientific research, there is hope that this vast amount of illness, death, and economic loss can be curtailed. By application of present knowledge and by acquisition of new knowledge in medicine and technology, U.S. scientists and their colleagues worldwide are seeking ways to prevent, relieve, and cure these diseases. It was in recognition of the magnitude of these problems and their potential for solution that the National Heart, Blood Vessel, Lung, and Blood Act (see Appendix) was passed by the Congress and signed by the President in 1972.

The passage of the Act and the initiation of the National Program have been important in many ways which are discussed throughout this report. Of great importance is the fact that the Program provides the public and the scientific and medical communities alike with tangible evidence that U.S. Government leaders realize the paramount importance of health for the future of our nation, and that they are taking steps to raise the health status of our citizens. Even more importantly, while most health programs in the past have focused strongly on the acute care of disease, this National Program focuses equally strongly on the importance of maintenance of health and on the prevention of disease. It recognizes the key roles that the individual and society as a whole play in implementing the goals set by the President and the Congress in enacting this legislation.

The Program provides a framework for collaboration between scientists in determining the underlying causes and means of managing these diseases, and the public in controlling environmental factors and personal habits that may increase the risk of these diseases. Because of the present and potential ability to control and cure the diseases involved, the Program could have an enormous impact on the nation's health.

The National Heart and Lung Institute (NHLI) and the scientific community it represents can provide the combination of vital factors needed to achieve the goals of the Program. They can provide almost three decades of experience, extensive research expertise, long established stability, highly trained and capable manpower, and an extensive pool of knowledge. During the past two years, the Institute and the scientific community have made rapid progress to meet the challenges and carry out the responsibilities presented in the legislation.

The Act significantly expanded the Institute's mandate and responsibilities. To implement these new and increased activities in an efficient and timely manner, the Institute made significant changes in its organizational structure, program management, and ways of communicating and collaborating with the public and the professional communities. The Institute was reorganized into five divisions. Three of these are categorical divisions: Division of Heart and Vascular Diseases, Division of Lung Diseases, and Division of Blood Diseases and Resources. The other two are the Division of Extramural Affairs and the Division of Intramural Research. Since the inception of the National Program, the Program Plan has undergone a series of revisions, and it will continue to change as new opportunities and needs are recognized. The current program elements are summarized in Table 1.

Table 1. National Heart, Blood Vessel, Lung, and Blood Program Structure

HEART AND BLOOD VESSEL DISEASES

1. Arteriosclerosis
2. Hypertension
3. Cerebrovascular Disease
4. Coronary Heart Disease
5. Peripheral Vascular Diseases
6. Arrhythmias
7. Heart Failure and Shock
8. Congenital and Rheumatic Heart Diseases
9. Cardiomyopathies and Infections of the Heart
10. Circulatory Assistance

LUNG DISEASES

1. Structure and Function of the Lung
2. Pediatric Pulmonary Diseases
3. Emphysema and Chronic Bronchitis
4. Fibrotic and Immunologic Lung Diseases
5. Respiratory Failure
6. Pulmonary Vascular Diseases
7. Inhalation Diseases
8. Respiratory Assistance

BLOOD DISEASES AND BLOOD RESOURCES

1. Bleeding and Clotting Disorders
2. Sickle Cell Disease and Other Disorders of the Red Cell
3. Biomaterials
4. Blood Resources

In accordance with the Act, an Office of Prevention, Control, and Education was established. Through this office and through its categorical program divisions, the Institute began to implement the prevention, control, and education programs provided for in the Act. During the past year, the Institute initiated three National Research and Demonstration Centers--one in each of the three categorical areas--in accordance with the provisions in the Act. The legislation considerably expanded the National Heart and Lung Advisory Council, both in its membership and in its responsibilities. In addition to reviewing applications for research funds, the Council plays an active role in the development, review, and evaluation of the National Program. Through a number of collaborative efforts with other institutes, agencies, and organizations, and through the Interagency Technical Committee mandated by the Act, the Institute has sought to utilize more effectively the national resources available for the Program. These collaborative efforts are discussed in Chapter III under the subheading "Program Coordination."

Some of the other new activities initiated in recent years which have significantly added to the Institute's program are:

- Development of an expanded program in lung diseases
- Coordination of the National Sickle Cell Disease Program
- Coordination of the National High Blood Pressure Education Program
- Collaboration in the implementation of the National Blood Policy efforts
- Implementation of large-scale clinical trials in arteriosclerosis, hypertension, and myocardial infarction
- Annual updating of the five-year National Program Plan and the development of this annual report to the President and the Congress.

The goals of the National Program were set by the 1972 legislation for the benefit of the nation as a whole. During the past two years, the Institute and the scientific community have attempted to respond to the legislative mandate.

This second annual report on the National Program covers calendar year 1974, and is the second update of the five-year National Plan. It supersedes Volume I of the original Plan submitted in May 1973* and the Plan presented in the First Annual Report of the Director, dated February 1974.**

The status of the National Program is presented for each of the three categorical areas. In each case the Program is discussed under five headings: Definition of Major Problem Areas; Research Programs; Prevention, Control, and Education Programs; Program Coordination; and Manpower Resources. The National Heart, Blood Vessel, Lung, and Blood Act of 1972 is reproduced in the Appendix.

*The National Heart, Blood Vessel, Lung, and Blood Program was presented in five volumes in May 1973: DHEW Publication Numbers are shown below:

Volume I.	National Heart and Lung Institute Summary (NIH 73-515)
Volume II.	Report of the National Heart and Lung Advisory Council (NIH 73-516)
Volume III.	Report of the Panel Chairmen (NIH 73-517)
Volume IV.	Panel Reports (NIH 73-518 - 73-521)
Volume V.	Program Analysis (NIH 73-522 - 73-524)

**National Heart, Blood Vessel, Lung, and Blood Program, First Annual Report of the Director of the National Heart and Lung Institute, February 13, 1974, DHEW Publication (NIH 74-514).

II. HIGHLIGHTS OF RECENT PROGRESS AND ACCOMPLISHMENTS

II. HIGHLIGHTS OF RECENT PROGRESS AND ACCOMPLISHMENTS

The purpose of the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423) was to:

> ". . . advance the national attack against diseases of the heart and blood vessels, the lungs, and blood . . . ."

The National Heart, Blood Vessel, Lung, and Blood Program was developed by the National Heart and Lung Institute and its advisors, according to the mandate in the Act. The initial Program Plan, which was forwarded to the President and the Congress in May 1973, presented a broad range of opportunities for improving the health of the American people. The strategy stated in that report continues to guide the implementation of the Program. It is:

> ". . . to marshall national resources for promoting and restoring health, and for preventing and treating diseases more effectively by:
>
> - Initiating an ordered sequence of coordinated program activities ranging from the acquisition of new knowledge to demonstration and control programs in the health care setting of the community
> - Providing adequate program evaluation for the application of existing knowledge to health care delivery systems
> - Evaluating the impact of implemented programs on the health of the people."

A comprehensive account of the status of the Program and the updated Five-Year Plan for all program areas addressed by the National Program is presented in Chapter III. Since this account is rather technical in content, highlights of prominent program developments are presented below for each of the three categorical areas. Follow-up actions are discussed in Chapter III.

HEART AND BLOOD VESSEL DISEASES

Arteriosclerosis —Improved Diagnosis

An intensive program has been launched to develop and assess new and improved instrumentation and techniques for noninvasive detection, characterization, and quantification of atherosclerosis. This instrumentation is urgently needed to assess treatments that may retard or reverse the disease. The instrumentation will also be of use in the early detection of arteriosclerosis before the clinical manifestations of the disease are present.

Heart Disease —Improved Diagnosis

A new diagnostic technique called echocardiography, which uses reflected ultrasound to provide a cross sectional image of the heart in three dimensions, is proving uniquely valuable in the diagnosis of a variety of congenital and acquired heart disorders. This highly effective technique is painless, noninvasive, and safe. It frequently provides information on structural abnormalities and their effects on heart performance which cannot be readily obtained by conventional X-ray techniques, such as angiography. In many instances, echocardiography may obviate the need for angiography, a procedure which may carry some hazard in critically ill patients.

Heart Disease —Diagnosis By Exercise ECG

The electrocardiographic (ECG) response to exercise has been considered a reliable screening test for detecting coronary heart disease that might not be evident from electrocardiograms recorded at rest. Recently, scientists evaluated the accuracy and sensitivity of ECG exercise tests in individuals undergoing extensive screening procedures for possible entry into one of the studies described in this report. Some subjects had clinical symptoms indicative of coronary heart disease; others did not. The tests yielded such high percentages of false-positive and false-negative results that their diagnostic value in the individual patient is in doubt, though they may be useful in epidemiological studies of large populations.

Premature Heart Disease —Prevention

In July 1973, after two years of extensive preparation and planning, the continent-wide network of Lipid Research Clinics and their support facilities began a study to determine whether reducing blood cholesterol levels in patients with Type II hyperlipoproteinemia (high blood lipids) could slow down or prevent the development of premature coronary artery disease. Recruitment of subjects for this seven-year trial was initiated during the second half of 1973. Healthy men, 35-59 years old with elevated cholesterol, are eligible. In 1974 almost 4,500 men participated in the first prerandomization visit, and many more thousands were screened. Over 800 have been randomized into drug or placebo groups. Completion of recruitment is projected for January 1976. Initially, physician and laboratory referral of prospective subjects was emphasized; more recently,

newer recruitment strategies are being used. These include industrial and blood bank screening, media support, and other more creative case-finding techniques.

Heart Attacks —Improved Detection of Risk Factors

Over the last two years the Lipid Research Clinics Program has evaluated available technology and developed with industry rapid, inexpensive, accurate, and precise methods for determining the level of certain blood lipids (cholesterol and triglyceride). They have demonstrated that accurate and precise values for blood lipids can be obtained by a group of high volume laboratories. This standardization is finding wide application in many clinical chemistry laboratories, thereby improving the accurate detection of one of the three major coronary heart disease risk factors. Standardization also assures the comparability essential for the success of the large-scale Lipid Research Clinic prevalence and prevention studies described later in this report.

Heart Attacks —Efforts to Decrease Risk

The purpose of the Multiple Risk Factor Intervention Trial (MRFIT) is to determine whether or not a preventive program directed at reduction of elevated blood lipids (cholesterol), reduction of high blood pressure, and reduction or elimination of cigarette smoking will result in a significant reduction in deaths from coronary heart disease. To determine their eligibility for participation in the MRFIT, over 150,000 men, aged 35-57, have been screened for coronary heart disease risk factors. Of this group more than 13,000 have increased risk of developing coronary heart disease and have expressed willingness to participate in this six-year research effort. Of these, 5,196 have met all eligibility criteria and have been enrolled in the primary prevention clinical trial. Twenty clinical centers in 14 areas of the country are carrying out the recruitment effort. The enrollment goal, i.e., 12,000 men with higher than average risk of developing heart disease, is expected to be reached during 1975.

Heart Disease —Improved Dietary Data Collection

A key element in a number of studies of the relationship of diet to heart disease is the collection and analysis of information on the eating habits of persons being studied. In 1974 the dietary data collection procedures for the Multiple Risk Factor Intervention Trial (MRFIT) and the Lipid Research Clinic Program were finalized. To insure comparability, identical dietary data collection procedures are being carried out in these two large-scale studies. A new open-ended food composition table, based on standard references, has been developed in a format designed to meet study needs. With the help of the U.S. Department of Agriculture, figures for fatty acids, carbohydrates, and dietary cholesterol have been verified or updated. Coding methods have been developed which allow for maximum automation. A central Nutrition Coding Center to process the dietary records of both studies is being established at the MRFIT Coordinating Center and a system for computerized calculation of recipes has been developed.

Heart Attacks —Treatment

Nitroglycerin, one of the oldest and best drugs for relief of the chest pain of angina pectoris, may also be uniquely valuable in the treatment of acute heart attacks. Recent animal experiments have shown that nitroglycerin reduces the extent and severity of heart muscle damage after blood deprivation. This is often a critical factor affecting survival, and also the amount of residual disability after recovery from heart attacks. Nitroglycerin was also shown to protect the heart against rhythm disturbances, a common and sometimes lethal complication. The drug is currently undergoing clinical evaluation in heart attack patients.

Heart Attacks —Reducing the Damage to Heart Muscle

Recent experimental studies have shown that when the blood supply to heart muscle is cut off by a heart attack the amount of heart muscle irreversibly damaged can be reduced by several different techniques. Reducing the workload of the heart by the very careful administration of drugs to slightly reduce the blood pressure, or by mechanical devices (the "intra-aortic balloon") have shown very encouraging results in limited clinical studies. Several promising drugs increase blood flow to the heart muscle, some by reducing swelling, others by dilating vessels. Others apparently alleviate coronary artery blockage by increasing diffusion of nutrients into the tissue. The provision of glucose in high concentrations in the presence of potassium and insulin provides a higher concentration of nutrients and seems to offer benefit as well. On the basis of these promising laboratory and clinical studies, an expanded program for protecting jeopardized heart muscle has been launched.

Heart Disease —Efforts to Decrease Mortality

Thirty Clinical Centers, a Coordinating Center, and an ECG Reading Center have been selected for the Aspirin-Myocardial Infarction Study. This is a randomized, placebo-controlled, double-blind study of the efficacy of aspirin in preventing mortality in men and women with documented coronary heart disease. Recruitment of 4,000 patients aged 30-69 will start early in 1975 and is scheduled to be completed by the end of the year. The patients will be observed for three years while on study medication.

Heart Surgery —Coronary Artery Bypass

The surgical placement of a bypass graft around a narrowed or occluded coronary artery has been extensively developed and widely practiced. Over 25,000 operations were carried out in the past year alone. In a substantial majority of patients with severe angina pectoris, the procedure results in relief of symptoms. However, the long-term effects as to length of life and the specific indications in other patients remain ill defined. Accordingly, a collaborative trial to assess these factors is going through the pilot phase stages preparatory to full-scale implementation.

Recurrent Heart Attacks —Evaluation of Therapy

Do drugs that reduce levels of certain blood lipids (cholesterol and triglyceride) confer any protection against recurrent heart attacks or improve long-term survival among men who have previously experienced one or more acute heart attacks? Apparently not, according to findings from the just completed Coronary Drug Project (CDP). This study was a nationwide collaborative trial. The primary objective was to evaluate the efficacy of five lipid-lowering drug regimens in the long-term treatment of coronary heart disease in men aged 30-64 with ECG evidence of previous heart attack. The 8,341 patients enrolled were randomly assigned to one of the six treatment groups including placebo in a double-blind fashion and were followed for a minimum of five years. Although the drugs lowered lipids, they did not benefit patients who had already sustained heart attacks. However, they may be of benefit when used to reduce the threat of first heart attacks in asymptomatic patients by intervening specifically against elevated blood lipids.

Heart Disease —Rehabilitation

The needs and opportunities for improved rehabilitation of patients with cardiac disease, particularly coronary heart disease, have been reported on by a task force following extensive review of the state of the art in this area. The report addresses itself to medical, psychological, and sociological factors needed to return the patient with coronary heart disease to his maximum potential following an acute heart attack.

Heart Disease —Specialized Centers of Research

For a number of years the Institute has supported a research program directed specifically at the improved understanding, prevention, and treatment of heart attack or myocardial infarction. The single largest part of this program has been the Myocardial Infarction Research Units. They combine broad programs of clinical research with fundamental laboratory studies and developments in relevant technology and investigative methods. Much of the improved understanding and treatment of heart attack, over the past five years, has come from these units which will complete their program in 1975. As an outgrowth of this program, the Institute implemented the broader program of Specialized Centers of Research (SCORs) on Ischemic Heart Disease. The objective of this program is multidisciplinary clinical and fundamental research directed at the reduction of death and disability from all forms of ischemic heart disease. This includes not only myocardial infarction, but also chronic forms of the disease such as angina pectoris, rhythm disturbances, and heart failure. The SCORs program is also directed at techniques of rehabilitation and problems of sudden cardiac death.

Heart and Blood Vessel Diseases —Animal Models

Progress in understanding the causes and in developing treatment for heart and blood vessel diseases has benefited greatly from animal research. The closer the animal models are to man the more likely it is that the results of studies will be helpful in studying the condition in man. Nonhuman primates are particularly useful models.

The Institute has embarked on a program to make nonhuman primate models of certain cardiovascular disorders available to investigators on a broad scale. This program, announced late last year, will cover breeding, supply, and study of several varieties of monkeys and baboons. Some of the animals will be given diets or other treatments to induce chronic atherosclerosis or hypertension. A search will also be made for animals with spontaneous disorders of lipid metabolism or blood pressure, and these will be studied both genetically and metabolically.

High Blood Pressure —National Education Program

In 1974 the National High Blood Pressure Education Program (NHBPEP) became fully operational. Nearly 100 national organizations cooperated in the planning and implementation of the first National High Blood Pressure Month in May 1974. As a result, over 400,000 persons were screened and the 76,000 with elevated pressures referred to a physician or clinic for further evaluation. During the High Blood Pressure Month, close to 10,000 articles on hypertension appeared in newspapers, and articles on hypertension were published in magazines and professional journals having a combined circulation of close to 4.5 million. During 1974 the Program secured free broadcast time equivalent to $4 million on television and over $200,000 on radio. In 1974 the High Blood Pressure Information Center answered more than 28,000 requests for information and published materials, and handled responses to over one-half million requests as a result of three newspaper columns by Ann Landers. In November 1974 the American Dental Association House of Delegates passed a resolution endorsing the NHBPEP and strongly encouraging continuing education in hypertension for dentists. The Program was similarly endorsed in December 1974 by the Office of Professional Standards Review Advisory Council which recommended to local Professional Standards Review Organizations (PSRO) a high priority for hypertension treatment and use of Program-developed guidelines.

High Blood Pressure —Education Research Program

Research was initiated in the spring of 1974 on new methods of educating the public and professionals about the problems of hypertension. Topics to be studied are: hypertension education for a low income community, improving patient compliance through nursing action, assuring patient compliance by methods such as health care contracts, and health education strategies for hypertension control. The results will be utilized to develop further the patient education component of the National High Blood Pressure Education Program.

High Blood Pressure —Behavioral Aspects

Many persons with high blood pressure are either unaware of their condition or are reluctant to embark on and adhere to treatment available for controlling it. One of the most important challenges, therefore, of the National High Blood Pressure Education Program (NHBPEP) is to devise approaches to modify the psychological and social factors that influence a person's adherence to a therapeutic regimen. In order to increase understanding of this problem, the

NHBPEP is embarking on a study of adherence behavior and the educational interventions that may enhance a patient's initial and long-term adherence to therapy.

High Blood Pressure —Benefits of Treatment

The Hypertension Detection and Follow-Up Program (HDFP) is a study to determine the benefits of high blood pressure control in the general population. The aim was to identify and enroll its goal of at least 10,500 persons with diastolic blood pressure of 95 mmHg or higher into a five-year study. The program has completed home screening for high blood pressure of over 160,000 persons. The program will assess the ability of long-term antihypertensive therapy to reduce mortality and morbidity from high blood pressure in persons aged 30-69. The results of this study are expected to show the potential for saving lives in the large number of persons known to be afflicted with this disorder. High blood pressure is found in 27 percent black males of this age group, 22 percent black females, 13 percent nonblack males, and 8 percent of nonblack females. Early data from one year of follow-up of the 11,500 participants reveal that 72 percent of those under continuing direct care of the HDFP clinics have had their blood pressure reduced to goal levels. Blood pressure levels have also been reduced for the group receiving regular care by physicians in the community at large.

High Blood Pressure —Periodic Variations

Blood pressure, blood electrolytes, and the output of hormones and other biologically active substances believed to be involved in the regulation of blood pressure are subject to circadian rhythms (periodic variations). The recent development of fast, accurate, and sensitive techniques for measuring these substances or the products of their metabolism in blood, urine, and other body fluids makes it possible to evaluate these rhythms more precisely. Their effects on blood pressure, and also on the results obtained with various therapies for hypertension, are presently under study. A fuller understanding of these rhythms promises to help in maximizing the effectiveness of drug therapy while reducing the incidence and severity of undesirable side effects.

High Blood Pressure —Possible Side Effects of Therapy

The Institute is cooperating with the Food and Drug Administration (FDA) in evaluating a reported association between use of reserpine and the occurrence of breast cancer. Reserpine is one of the oldest effective medicines to reduce high blood pressure, has been used for over 20 years, and has been a mainstay of antihypertensive therapy in many thousands of individuals. Preliminary examination of the data found in three retrospective case-control studies has led to the conclusion that significant problems or deficiencies exist in the nature of such hospital case-control data which do not allow conclusive judgment of the results of these studies. The FDA is convening an expert panel to review the data and, if necessary, to recommend research or data collection efforts to resolve the issue. Meanwhile, the Institute has recommended that the use of reserpine

be continued according to the protocol in the Hypertension Detection and Follow-Up Program and that women on the study both be alerted to the reported findings and offered the choice of being removed from reserpine therapy.

High Blood Pressure —Animal Models

A strain of rat has been bred that is genetically hypertensive, and a subgroup of this strain is especially prone to stroke as a result of hypertension. A monograph is being developed on the appropriateness of the genetically hypertensive rat as the best animal model of human essential hypertension, and to establish breeding, care, and maintenance guidelines for these animals and appropriate control rats with normal blood pressure. To provide standardized breeding stock for scientists throughout the world, the Institute has coordinated the establishment of a resource colony of stroke-prone rats by the National Institutes of Health's Division of Research Services.

Heart Assist Devices

Progress continues in developing materials, components, and systems for circulatory assist and cardiac replacement or artificial heart devices. No totally satisfactory synthetic material has been developed for long-term use in implanted devices, but a number of leads are being followed, and continued progress is being made in improving the compatibility of several types of materials and surfaces with blood. The energy systems needed to power implanted devices are also under investigation. Improvements in efficiency, performance, and endurance have been achieved. One indication of progress is the experimental replacement of the heart of a calf by an artificial heart which operated satisfactorily for over three months.

LUNG DISEASES

Respiratory Failure —Diagnosis

A primary complication of respiratory failure is a low oxygen content in the blood, despite the presence of normal oxygen in the inhaled air (a condition called hypoxic hypoxia). Because of the dire consequences of low blood oxygen, a recently developed technique for prompt and rapid identification of physiologic changes that are associated with hypoxic hypoxia and the extent to which they contribute to the patient's condition, offers great promise. Although still in the developmental phase, the technique has given encouraging results at several centers and should lead to therapy that can be directed to the causes (rather than the effects) of hypoxic hypoxia.

Respiratory Failure —Treatment

An artificial lung, which causes minimal damage to the cells and chemical components of the blood, has been developed to the point

that it is being tested clinically. Called a membrane oxygenator, this device is considered a promising addition to the methods available for treating respiratory failure. Its use is based on the assumption that if the patient can receive respiratory assistance, without the threat of oxygen toxicity, during the most critical phase of the respiratory crisis, it may be possible for the lung to recover to the point that auxiliary oxygen will not be needed. Nine centers are participating in an evaluation of the membrane oxygenator as a therapeutic tool.

Respiratory Failure —Diagnostic Device

A device that can monitor continuously the level of blood gases over prolonged periods is essential to both diagnosis and assessment of the efficacy of treatment of respiratory failure. Such a device has now been designed. It holds great promise on the basis of animal studies, although some problems associated with its use remain to be resolved. When ready for clinical use, its impact on both diagnosis and assessment of treatment should be of great importance.

Respiratory Distress Syndrome —Improved Understanding

In both adults and infants, respiratory distress syndrome, an often fatal respiratory condition, is associated with lack of surfactant, a material produced in the lungs. Alterations in surfactant production or secretion also play a role in oxygen toxicity (a possible consequence of treatment with oxygen) and pulmonary edema, an accumulation of fluid in the lung that is associated with a number of pulmonary disorders. Fundamental studies of surfactant production, secretion, and biochemistry are elucidating its role in these disorders. Activation and release of surfactant are affected by mechanical stresses of the kind that occur during assisted ventilation, a finding of considerable importance in view of the wide therapeutic use of ventilatory assistance.

Neonatal Respiratory Distress Syndrome —Prenatal Diagnosis

The premature infant is prone to a form of respiratory insufficiency called hyaline membrane disease (neonatal respiratory distress syndrome). Because risk of death is high, early diagnosis of infants with hyaline membrane disease is of paramount importance. The chemical precursors of surfactant have been identified, and it is now possible to predict whether an infant's lungs are likely to be incompletely developed at the time of birth. This is done by analysis of samples of amniotic fluid, which surrounds the fetus in the uterus. When these tests indicate insufficient surfactant production, the risk of hyaline membrane disease is high. These studies have thus provided a tool that permits prenatal diagnosis and hence the opportunity for therapy immediately after birth.

Neonatal Respiratory Distress Syndrome —Treatment

Until recently, infants with hyaline membrane disease could only be successfully treated in centers where specially trained staff used highly sophisticated techniques. One of these techniques, the use of carefully applied positive pressure (continuous positive airway

pressure) to inflate the collapsed lungs, has recently been refined through research. The technique can now be safely used even in small hospitals remote from major academic medical centers. As use of the technique becomes widespread, there should be marked improvement in survival rates of infants with hyaline membrane disease.

Lung Fibrosis —Improved Understanding

A number of pulmonary diseases are characterized by excessive growth of certain types of cells, particularly the cells of lung connective tissue. Collagen, the substance that provides strength to the normal lung, but which may be produced in excess in some lung diseases, is being extensively studied. Chemical investigation has demonstrated that collagen in the lung resembles collagen from other organs. The specific lung cells--fibroblasts--that produce collagen have now been grown outside the body in tissue cultures and have been shown to synthesize collagen in a pattern that is similar to that which occurs in the lung itself. These findings are an important step to further investigation of the components of connective tissue and how they are modified in diseases of the lung.

Allergic Lung Diseases —Improved Understanding

The most commonly known allergic disease of the lung is asthma, but there are a large number of other pulmonary disorders (the hypersensitivity lung diseases) that occur after exposure to a variety of airborne compounds. The study of substances that, when inhaled, induce allergic responses reflected in hypersensitivity lung diseases, is providing insights into how such adverse responses can be avoided or controlled. Results suggest that when persons are exposed to toxic airborne agents, these agents induce constriction of the airways, thus trapping the substances that cause allergic reactions and preventing the action of body substances that normally counteract the effect of the inhaled material.

Allergic Lung Diseases —Diagnosis

The simplest way to prevent allergic lung diseases is to avoid exposure to substances that will elicit hypersensitivity reactions. However, not all persons exposed to the toxic pollutants in the air develop hypersensitivity lung diseases; therefore, it is important to identify those who are susceptible to such diseases before they are exposed. Until recently the tests for determining hypersensitivity were very nonspecific. Now, specific substances have been developed that can be used to test individuals to determine which substances will provoke a hypersensitivity response. This is a valuable diagnostic tool that will help to prevent these diseases.

Lung Diseases —Improved Understanding

The lung--one of the most heterogeneous organs of the body--has approximately 40 different types of cells, each with a specific function that may be altered in disease. As an initial step toward identifying the role of each cell type and how its function is altered in disease, numerous studies are concerned with developing methods of separating lung cells and investigating their cellular

components and biochemistry. Isolation of "Type II cells" of the alveoli (air sacs) is of special interest at this time because these cells (1) have a role in repair of the injured lung, dividing and replacing other types of cells that may be damaged, and (2) secrete surfactant, a substance that is essential to prevent collapse of alveoli. In some laboratories work has progressed to the point that uniform preparations of Type II cells both from normal and diseased lungs are being studied at the chemical level. Extension to other cell types of the current techniques for separation and isolation will have an impact on understanding a variety of lung diseases.

Lung Diseases —Needed Manpower Development

The Institute has announced competition for the new National Pulmonary Faculty Training Program. This program is intended to strengthen pulmonary faculties at schools of medicine and osteopathy which have not yet developed adequate programs in respiratory disease. Junior faculty members from schools wishing to strengthen their pulmonary academic programs will be provided the opportunity of obtaining extensive pulmonary training at medical centers with strong academic programs. After the formal training, the junior faculty will return to the school that sponsored the training, and develop a program of research, teaching, and clinical care in respiratory diseases and disorders.

Lung Diseases —Dissemination of New Knowledge

The establishment of a National Research and Demonstration Center at the University of Vermont College of Medicine will tie together and intensify efforts and resources for the control of respiratory disease in Vermont (a state with one of the highest respiratory ailment rates in this country). A primary function of this Center will be to close the gap between new medical knowledge and its distribution and application. This means that, through a regional management structure, physicians, nurses, and allied health personnel will be brought up-to-date on important treatment information soon after that information is known.

Lung Diseases —Young Investigators

The Young Investigator Pulmonary Research Grant Program, recently initiated by the Institute, is intended to foster the pulmonary research interests of young scientists and physicians by providing them with modest, independent support for a project of their own design. It will encourage young investigators, in basic science disciplines, to channel their interests to pulmonary disease-related research. At the same time it will welcome participation by investigators in clinical disciplines. The first competition has, to a noteworthy extent, achieved these objectives. Fifty percent of the applications are from institutions that have never or only rarely received support from the National Heart and Lung Institute.

BLOOD DISEASES AND BLOOD RESOURCES

Blood Clots —Detection

New procedures, employing radioisotope labeling of coagulation proteins and platelets, have been useful in the detection and localization of venous thrombosis (blood clots in the veins). These techniques are combined with noninvasive methods for measurement of blood flow and special X-ray procedures in clinical studies. Some promising new assays of fibrinogen (a blood protein) metabolic products have been developed and may provide tools for the detection and quantitation of intravascular clot formation.

Blood Clots —Treatment and Prevention

Venous thrombosis is a frequent complication in patients undergoing surgery, especially orthopedic surgery. Current clinical trials will determine the effectiveness of heparin and platelet-inhibiting drugs in preventing venous thrombosis and will also help define the high-risk populations that might benefit from such treatments.

National Blood Banking

Several studies were recently completed and published on the development of a Nationwide Blood System. These include cost-finding methodologies adaptable to blood banking communities which can form a basis for establishing uniform rational pricing policies, analysis, and design for a National Blood Resource Information System and a report on regionalization in present blood supply systems.

Safety of Blood Therapy

Blood transfusions are important in saving lives. They may also transfer diseases, such as hepatitis, unless great care is taken in collection, preparation, and storage of the blood intended for transfusion. New techniques have been developed for inactivation of hepatitus B virus in various blood fractions. If these techniques are successfully applied, the risks of hepatitis may be significantly reduced.

Frozen Blood —Improved Utilization

The development of a closed system docking device for use with thawed frozen blood transfusion preparations is now at the stage of clinical testing prior to licensure by the Food and Drug Administration. Successful use of such sterile connecting devices by the nation's blood system should allow an extended lifetime of thawed preparations and thus reduce the wastage of blood resources due to outdating of these preparations before they can be transfused.

Transplantation Graft Rejection

Presensitization to transplantation antigens as a result of prior blood transfusions appears to play a contributory role in graft rejection by transplant patients. Preliminary evidence from Institute-supported clinical studies indicates that this increased rejection is less likely to occur in patients receiving thawed frozen blood than those receiving leukocyte-poor (low numbers of white blood cells) blood prepared by centrifugation.

Hemoglobin Disorders —Improved Understanding

Scientists have developed cell-free systems for protein synthesis that duplicate in the test tube both normal hemoglobin synthesis and the disturbances in hemoglobin production responsible for such hereditary blood disorders as Cooley's anemia and sickle cell disease. The systems permit the various components involved in hemoglobin production to be manipulated at will. This, in turn, makes it possible to study the contribution of each component to the production of regulatory processes, to identify the causes of various hemoglobin disorders, to define the nature of defects, and to seek out and evaluate potential approaches to the correction or amelioration of associated clinical disease problems.

Cooley's Anemia —Improved Understanding

In Cooley's anemia, the basic defect is a relative shortage in red blood cells of the genetic material, called betaglobin mRNA. This material directs the assembly of one of the two protein chains that are combined to form the hemoglobin molecule. As a result of this shortage, beta-chain synthesis is much slower than usual, while alpha-chain synthesis proceeds at a normal rate. The result is a large excess of alpha-chains, which eventually precipitate in the red blood cells and cause their premature destruction. Hence, persistent anemia results and can currently be corrected only by periodic blood transfusions. Now that the basic defect in Cooley's anemia has been identified, scientists are seeking possible means of stimulating increased betaglobin mRNA synthesis during the development of red blood cells. This might permit correction of the underlying cause of this blood disorder, the imbalance between alpha- and beta-chain production.

Blood Diseases —Improved Understanding

In two major hereditary blood diseases--Cooley's anemia and sickle cell disease--the problem resides in the beta-chain of hemoglobin. In Cooley's anemia, beta-chain production is abnormally slow; in sickle cell disease, the beta-chain is flawed. Both abnormalities have serious clinical consequences for the victim. Humans have the genetic capability to produce more than one kind of hemoglobin. The hemoblogin found in fetal red blood cells (hemoglobin F) in contrast to that in adults (hemoglobin A) does not contain the beta-chain. Hemoglobin F is a perfectly serviceable form of hemoglobin, but a genetic switch to hemoglobin A production normally occurs shortly after birth. In goats and certain species of sheep, three forms of hemoglobin are produced in the course of normal development: hemoglobin F, an intermediate form called hemoglobin C, and hemoglobin A. A genetic switch from hemoglobin A to hemoglobin C production can be achieved by making the animals anemic. This can also be done in a limited way in the test tube by exposing bone marrow cells to high concentrations of the hormone erythropoietin. The mechanisms of this genetic switching are under study as are various agents that may induce a switch in production from one form of hemoglobin to another. Similar studies are planned with human marrow cells to determine whether these cells can be induced to switch from adult to fetal hemoglobin synthesis. Activation of hemoglobin F

synthesis in the cells of subjects with sickle cell disease or Cooley's anemia may well alleviate the symptoms of these diseases by eliminating the beta-chain problems.

Sickle Cell Disease —Screening and Education Clinics

To reduce the painful, crippling, and possibly life-threatening effects of sickle cell anemia, the Institute supports screening and education clinics administered by the Sickle Cell Disease Office, Bureau of Community Health Services, Health Services Administration. This program serves to develop and field-test methods of carrying out service activities, including increased public awareness, education, screening, counseling, and patient referral under various circumstances in a variety of environments. During the past year some 26 screening and education clinics were in operation. During that period approximately 400,000 individuals were screened for evidence of sickle cell and approximately 1 in 10, or 40,000, were found positive for sickle cell trait, were given appropriate counseling on the nature of the problem, and were referred to appropriate services. In addition, the Comprehensive Sickle Cell Centers supported by Institute grants have screened over 100,000 individuals, of whom approximately 10,000 were counseled and referred to appropriate services.

Sickle Cell Disease —Diagnosis and Treatment

To successfully deal with the sickle cell problem, there is a need to provide more accurate, less expensive, and less time consuming methods to identify abnormal hemoglobins in patients being screened. Preliminary studies using microcolumn chromatography suggest that this approach may provide a useful, quick, and accurate tool for the identification of sickle and several other abnormal hemoglobins. The early identification of eye lesions and their treatment may significantly reduce blindness and other visual complications in sickle cell disease. New photographic contrast techniques have been developed for better detection of such lesions. Various modifications of treatment, including argon and xenon photocoagulation, are currently underway.

Biomaterials —Development and Evaluation

Several special plastic materials have now been developed which have mechanical properties that imitate many of the features of living tissues. These materials are being evaluated for their possible use in a variety of prosthetic applications, including blood vessel replacements and artificial heart valves. Extensive work has been carried out on surface-grafted hydrogel systems which show promising blood compatibility. Clinical trials of these materials are now timely.

III. STATUS OF PROGRAM AND UPDATED FIVE-YEAR PLAN

III. STATUS OF PROGRAM AND UPDATED FIVE-YEAR PLAN

The current status of the National Heart, Blood Vessel, Lung, and Blood Program and the Plan for its conduct over the next five years are presented in this chapter for each of the major areas: Heart and Blood Vessel Diseases; Lung Diseases; and Blood Diseases and Blood Resources. A standard pattern is used to permit quick location of the subprograms, problems, and activities within the National Program.

- First, general background information on NHLI program development is provided.

- Second, a conceptual framework of the principal components and functions of the cardiovascular, pulmonary, and blood systems together with definitions of the major problem areas encompassed in the National Program are presented in nontechnical language. This conceptual framework is provided to help the nonspecialist better understand the progress, problems, and plans, and to evaluate the progress.

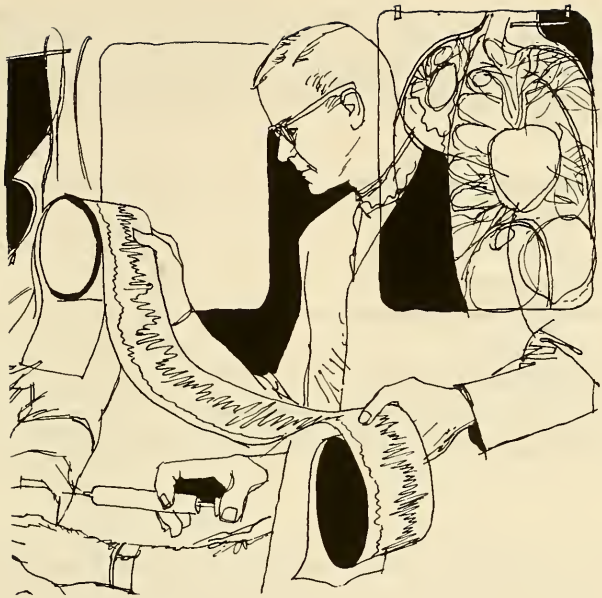
- Third, the current status and an updated five-year plan for NHLI research programs are presented for each of the problem areas. In each case detailed information is provided on program goals, program status (recent progress and future challenges), and program plans (actions and proposed schedules).

- Fourth, the current status and updated five-year plan for NHLI prevention, control, and education programs are summarized.

- Fifth, NHLI long-range plans for manpower development are discussed.

- Sixth, the Institute's major cooperative and collaborative efforts with other public and private organizations for the advancement of the National Program are highlighted.

This report builds on information provided in the initial Program Plan and the First Annual Report of the Director of the National Heart and Lung Institute which in turn updated the initial Program Plan.



HEART AND BLOOD VESSEL DISEASES

Cardiovascular diseases (heart and blood vessel diseases) continue to be the primary health problem in the United States. It is estimated that 28,000,000 Americans are afflicted with some form of heart or blood vessel disease: 23,000,000 of them have hypertension, 3,900,000 suffer from coronary heart disease and 1,700,000 from rheumatic heart disease, while 1,650,000 have had one or more strokes. In 1972, an estimated 1,060,000 Americans died from heart and blood vessel diseases; this represented more than 54 percent of deaths from all causes.

The Institute's initial plans to develop and coordinate a National Program in cardiovascular diseases were presented in the National Heart and Lung Institute Summary (Volume I) of the National Heart, Blood Vessel, Lung, and Blood Program, May 1973.

A review and assessment and a revised five-year program plan appeared in the First Annual Report of the Director of the National Heart and Lung Institute, dated February 13, 1974. In this Second Annual Report of the Director, the updated National Program in heart and blood vessel diseases is presented in 10 program areas similar in scope to those outlined in the first annual Director's report:

1. Arteriosclerosis
2. Hypertension
3. Cerebrovascular Disease
4. Coronary Heart Disease
5. Peripheral Vascular Diseases
6. Arrhythmias
7. Heart Failure and Shock
8. Congenital and Rheumatic Heart Diseases
9. Cardiomyopathies and Infections of the Heart
10. Circulatory Assistance.

In response to the enabling legislation, the National Heart and Lung Institute continues to develop and support an integrated program embracing fundamental and clinical research and manpower development and training to satisfy projected needs. It supports prevention, control, and education activities to provide for efficient and timely application of knowledge obtained through research. The Institute employs all appropriate available support mechanisms such as investigator-initiated research projects, program project grants, Specialized Centers of Research (SCORs), a National Research and Demonstration Center, targeted research and development contracts, and intramural research to develop and support its cardiovascular programs.

Program goals, evaluations, and plans are updated in this second annual report. The updated Program Plan for the next five years is based upon an evaluation of recent progress and future challenges as identified by the Institute, its advisors, and the scientific community. These plans are presented as planned actions and schedules.

Before discussing these scientific aspects of the National Program, a summary description is presented (in italics) of the cardiovascular system and the major problem areas within the National Program.

DEFINITIONS OF MAJOR PROBLEM AREAS

This section provides a framework in nontechnical language to help the nonspecialist understand the subsequent discussions of specific cardiovascular programs. It summarizes:

1. *The cardiovascular system: Its components and functions*
2. *Major problem areas.*

1. THE CARDIOVASCULAR SYSTEM: ITS COMPONENTS AND FUNCTIONS

The cardiovascular system is composed of the heart and blood vessels (arteries, arterioles, capillaries, venules, and veins) which transport the blood throughout the body. An adequately functioning cardiovascular system is of vital importance to all parts of the organism since this is the system which supports the life and function of each of the many billions of individual cells which make up the human body.

Living cells are complex biochemical factories which convert oxygen and nutrients into carbon dioxide and waste products and use the energy released by these processes to produce the many different kinds of chemicals and biochemicals needed to sustain their various functions. To do this effectively, the cells require a relatively stable liquid environment. In the case of single-celled animals which live in an environment of water, the transfer of important substances in and out of the cells is a relatively simple process. The cells simply absorb the nutrients and oxygen directly from the surrounding water and similarly discharge their waste products directly into the same surroundings. In more complex organisms, such as man, with billions of cells organized into different organ systems, the stable liquid environment required by the cells is maintained by a complex cardiovascular system which has evolved to transport substances to and from the cells via the blood.

The human heart (see Figure 2) consists of two pumps working in unison to circulate the blood through the two major components of the cardiovascular system: the systemic and the pulmonary circulations. The systemic circulation is a high pressure system which carries blood from the heart to all parts of the body and returns it to the heart; the pulmonary circulation is a low pressure system which carries blood from the heart to the lungs and returns it to the heart. A schematic representation of the human cardiovascular system is shown in Figure 3.

The two heart pumps are separated from each other by a vertical partition or septum and each pump is further divided into an upper and lower chamber connected by one-way valves to prevent the blood from flowing backwards. The upper chambers are called atria and the lower chambers are called ventricles.

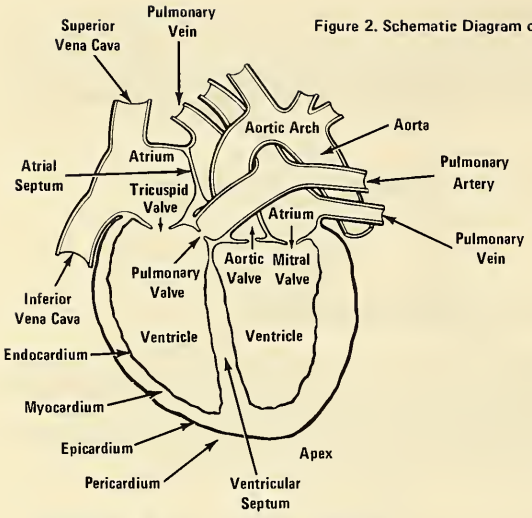


Figure 2. Schematic Diagram of a Cross Section of the Human Heart

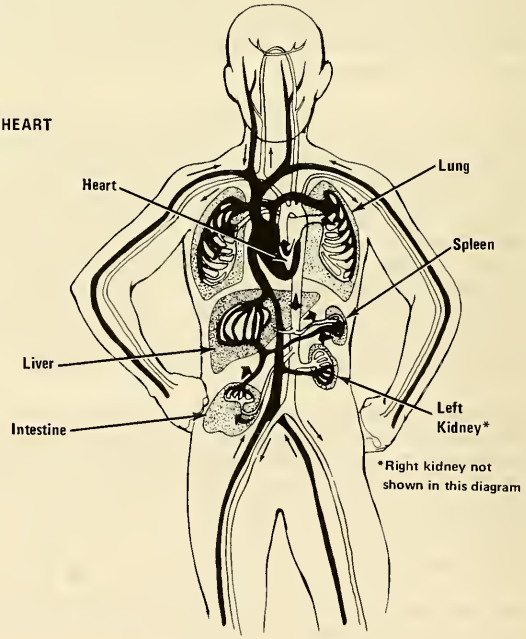


Figure 3. Schematic Diagram of the Human Cardiovascular System

To prevent the blood from flowing backwards there are one-way valves situated where the major arteries emerge from the heart. The blood returning to the heart from all parts of the body enters the right atrium through two major veins, the superior and inferior venae cavae. From the right atrium the blood is pumped into the right ventricle which, in turn, pumps it through the pulmonary arteries to the lungs. The blood from the lungs returns to the left atrium via the pulmonary veins, and is pumped through the left ventricle to the aorta which branches into arteries leading to different parts of the body.

The arteries divide into smaller and smaller branches and eventually into arterioles. Finally, the blood passes into the capillaries which are tiny blood vessels, just big enough for single blood cells to pass through one by one. Every cell in the body is close to a capillary and it is here that the real work of the cardiovascular system takes place. The liquid environment required by the cells is provided by the capillaries in the following manner. As the blood flows through the capillaries, some of the fluid from the blood, containing nutrients and oxygen, passes through the capillary walls to bathe the adjacent body cells. Similarly, fluid containing waste products and carbon dioxide is returned from the cells to the cardiovascular system either through the capillary walls or through another system of vessels called the lymphatic system. The normal metabolic processes of the cells cause an exchange of about one-third of the oxygen carried in the blood for carbon dioxide.

The cardiovascular system is intimately coupled with the respiratory system for gas exchange and with the kidney and liver for waste removal. After the blood has passed through the capillaries and picked up waste materials and carbon dioxide, it enters the veins which lead it back to the heart. As the blood passes through the lungs, the carbon dioxide is exchanged for oxygen and the fully oxygenated blood is returned to the left atrium. The blood is then pumped out into the systemic arteries again via the left ventricle to start on another circuit through the body. During the systemic circuit some of the blood passes through the kidneys and the liver where metabolic waste materials are removed.

At any given time the physical characteristics of the blood vessels can vary widely depending on the needs of the whole body and the particular organ or cells which they supply. Blood pressure, blood flow, and blood oxygen content of vital organs such as the brain, heart, and kidneys are kept within narrow physiological limits by a complex control system. This control is both via the interaction of the autonomic (involuntary) nervous system and numerous hormones (chemical messengers) circulating in the blood. Overall control of both the autonomic tone and the hormone concentrations of the cardiovascular system is exerted by the complex interaction of several sensors, some sensitive to blood pressure and others to the chemical composition of the circulating blood, mainly its oxygen content and its acidity. The major sensors are strategically situated to sample the pressure and chemical content of the oxygenated blood just as it leaves the left ventricle. There are also sensors in the brain, kidney, and other parts of the body.

Heart muscle (myocardium) is a unique type of tissue. It is a syncytium, that is, each cell is connected by a bridge to its neighbor. The heart muscle

syncytium contracts periodically at a rate of about 70 times per minute in resting man, forcing the blood throughout the body. These periodic contractions are initiated through a natural pacemaker system situated in the heart. This system generates electrical impulses which spread through the atria and the ventricles in a uniform predetermined manner. As a result, in the healthy heart the four chambers contract and relax in a coordinated manner, making the heart a very efficient pump.

The contractions of the heart muscle are not voluntary. Throughout life the heart continues to operate spontaneously and almost totally beyond our control. The pacemaker system is controlled by a complex set of feedback mechanisms involving nerves, hormones, and receptors for pressure, oxygen content, acidity, and concentrations of various substances in the blood as well as other factors. The heart sends the blood rapidly through the body under high pressure, and during each 60 seconds, the same blood has passed throughout the body at least twice.

The arteries have thick walls composed of three layers. The innermost layer, in contact with the flowing blood, is very thin, smooth, and glistening. The middle layer contains largely muscle fibers and elastic tissue while the outer layer is a tough fibrous coat which strengthens the vessel and prevents it from over stretching. The inner space of blood vessels through which the blood flows is the lumen. The coronary arteries (Figure 4) supply blood to the heart muscle. The status of these arteries plays a very important role in coronary heart disease. A decrease in the lumen or a complete blockage of these arteries or their main branches may result in serious consequences such as heart attack, heart failure, and death.

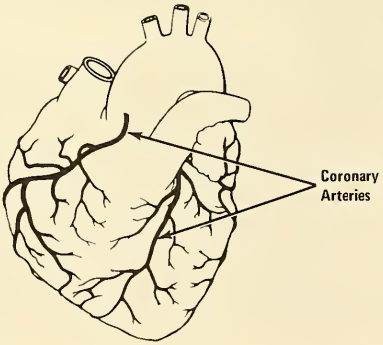


Figure 4. External View of the Human Heart Showing the Normal Coronary Circulation

The veins, like the arteries, have three layers, but compared to the arteries the middle and outer layers are quite thin and contain very little muscle or elastic tissue. Capillaries have very thin walls, one cell thick. Their walls act as so-called semipermeable membranes through which fluid and certain substances can pass back and forth between the blood and the body cells.

The force exerted against the walls of blood vessels by the blood flowing through them is the body's blood pressure. This pressure is highest in the arteries just as they emerge from the ventricles, gradually decreases in their branches, drops sharply in the arterioles, further in the capillaries, and is lowest in the veins returning the blood to the heart. Blood pressure is normally expressed in millimeters of mercury and is measured in a large artery such as in the arm. The measurement consists of two numbers: the higher is the arterial pressure recorded during the heart's pumping stroke, or systole, and is the systolic blood pressure. The lower number represents the arterial pressure prevailing while the heart relaxes and refills between beats. This is the diastolic pressure.

While blood pressure tends to be maintained at a constant level, it usually rises slightly with increases in the heart's output of blood and it also varies with changes in blood vessel tone. The vessels exerting the most pronounced effect on blood pressure are the smallest arterial branches, the arterioles. Contraction of the muscle fibers of the walls of the arterioles constricts these vessels. This increases their resistance to blood flow and thus increases blood pressure, much as shutting down the nozzle on a garden hose increases the water pressure in the hose. Conversely, dilation of the arterioles increases their capacity, reduces resistance to blood flow, and so tends to reduce blood pressure. However, these changes in the resistance of arterioles are usually to compensate for local blood flow needs; as one goes up the other goes down. The net result is that the blood pressure undergoes relatively small changes. The arterioles are sometimes called resistance vessels because changes in their tone lead to changes in blood pressure both in health and disease.

The autonomic nervous system is the involuntary nervous system. It regulates many tissues and functions not under conscious control, including heart beat, blood pressure, and blood vessel tone. It consists of two divisions, the sympathetic and parasympathetic, which usually have opposing effects. Sympathetic stimuli tend to increase heart rate, constrict blood vessels, and raise blood pressure. Parasympathetic stimuli reduce heart rate, relax blood vessels, and lower blood pressure. Normal blood vessel tone (moderate constriction) is maintained largely by the activity of the sympathetic division of the autonomic nervous system.

Blood pressure is monitored by sensors called baroreceptors and chemoreceptors, situated near the large arteries where they leave the heart. Baroreceptors detect changes in blood pressure and act through the autonomic nervous system to keep the pressure within normal limits. When blood pressure rises above or falls below these limits, the baroreceptors attempt to bring it back within the normal range. The chemoreceptors which are sensitive to the oxygen content and the acidity of the blood exert control not only over respiration but also over blood pressure. Acting through the autonomic nervous system, both

sensor types modify blood pressure via appropriate changes in heart performance and in the caliber of the resistance vessels.

Heart performance and blood pressure are also profoundly affected by certain hormones of the adrenal glands, notably by norepinephrine and epinephrine. Both of these hormones are powerful heart stimulants and blood vessel constrictors. Both are secreted in increased quantities during vigorous exercise and also during fright or other severe emotional stresses. Other hormones that play a major role in the regulation of blood pressure are the kallikrein-kinin system, the renin-angiotension aldosterone system, and the prostaglandins. The major chemical transmitter of the sympathetic nervous system, norepinephrine, and that of the parasympathetic nervous system, acetylcholine, raise and lower the blood pressure respectively. Two other naturally occurring substances, serotonin (5-hydroxytryptamine) and histamine also act on cardiovascular tone. The actions of the former are very complex; those of the latter lead to a fall in blood pressure.

Thus, a number of mechanisms operate in the regulation of heart performance and systemic blood pressure making adjustments as necessary to meet the shifting circulatory needs of the organs and tissues of the body.

2. MAJOR PROBLEM AREAS

For more than fifty years, heart and blood vessel diseases have been the major cause of death in this country. They now account for 54 percent of all deaths annually. This is more than three times the death rate from cancer, the next highest cause. An estimated 28 million Americans have diseases of the heart and blood vessels, resulting in a large burden of acute and chronic illness and disability. Hence, there is reason for referring to heart and blood vessel diseases as the modern epidemic. Moreover, heart and blood vessel diseases cost the economy more than $30 billion per year in lost productivity and expenses for medical care.

Of the 10 major problem areas, arteriosclerosis and hypertension are considered the major fundamental cardiovascular disease problems in the United States; some of their major manifestations are coronary heart disease, cerebrovascular disease, arrhythmias, heart failure, and shock. Although we have an understanding of many of the associated conditions and disordered mechanisms that predispose to arteriosclerosis and occur in hypertension, the fundamental causes of arteriosclerosis and most causes of hypertension are unknown.

Arteriosclerosis

Arteriosclerosis, or "hardening of the arteries," is by far the most common of the serious diseases affecting man in Western society. It represents a chronic progressive pathologic change in which the inner lining of the arteries becomes rough, thick, hard, and covered with lipid-rich plaques. Eventually, the inner diameter of the vessels decreases and blood flow in the diseased arteries diminishes or stops completely. Arteriosclerosis begins early in life and

generally becomes manifest in middle age or later. Until it does become manifest as heart attack, stroke, or other illness, it is often without symptoms and is therefore undetected. Its first clinical manifestation may be an abrupt catastrophic illness.

Virtually all adult American males and post-menopausal women are afflicted to some degree. The economic impact of arteriosclerotic disease in the United States has been estimated at $26 billion per year in lost productivity and expenses for medical care. If arteriosclerosis could be prevented, hundreds of thousands of lives might be prolonged. International statistics reveal a great variation in death rates for atherosclerotic coronary heart disease. For instance, in Denmark and Sweden, the death rate for men under the age of 55 is less than half that for the same age group in the United States; in many countries it is far lower and in some, for example Japan, atherosclerotic coronary disease is a rare condition. This difference indicates that the high death rates due to arteriosclerosis in the United States are neither necessary nor inevitable. Although attempts to learn why the United States fares so poorly in these comparisons have not been conclusive, studies have suggested that differences in diet, lifestyle, and personal habits may be important. Risk factors associated with an increased rate of development and progression of arteriosclerosis are age, sex, high levels of cholesterol in the blood, high blood pressure, and smoking. Of these, the latter three can potentially be controlled, and considerable effort is currently being expended in the National Program to learn more about these as well as other factors which may play a role in the development of atherosclerosis.

Hypertension

Hypertension, or high blood pressure, is a common and often serious condition. An estimated 23 million adult Americans, or about 15 percent of the adult population, have some degree of hypertension. It is more common in the black population than in the white population. It predisposes to arteriosclerosis and is a risk factor for heart attack and heart failure, and it is the major predisposing factor for stroke.

Hypertension can be treated, and treatment reduces the incidence of stroke, kidney failure, and heart failure. However, it is uncertain at present whether treatment will also reduce the incidence of heart attacks. It is also uncertain whether slight or mild degrees of hypertension require treatment. Current treatment, while effective, is unsatisfactory in that it requires lifelong adherence to medication, is expensive, has some side effects, and must be individualized. In more than nine out of ten cases of hypertension, the cause of the disorder is unknown and hence we still lack the means to prevent or cure it even though treatment and control are possible.

High blood pressure is easily detected, but may exist for many years without symptoms. While it can be controlled with available therapy, of the millions of Americans with this disease, half are probably unaware that they have it, and of those who are aware, less than half are receiving adequate therapy. The National Program is expending efforts both on research to discover the causes of hypertension and on programs to educate the public about the dangers of hypertension and the benefits of treatment.

Cerebrovascular Disease

Cerebrovascular disease occurs when an artery supplying blood to the brain is blocked, ruptured, or injured. Cerebrovascular disease due primarily to arteriosclerosis and hypertension is the basis for the great majority of strokes. The individual and public health burden of death, paralysis, and brain damage from cerebrovascular disease is large. Of the 1.7 million adults who have this disease, 800,000 are partially or completely disabled and 200,000 reside in nursing homes. Stroke kills about 200,000 persons a year particularly at older ages. The death rate is greater among men than women, and greater among blacks than whites. Each year, nearly 600,000 patients are discharged from our hospitals with a diagnosis of stroke, and each year about 250,000 individuals between the ages of 25 and 64 are crippled mentally or physically by a stroke. Many more lives could be saved and disabilities prevented if we had effective methods for prevention and treatment of arteriosclerosis and hypertension, and if available treatment were more widely applied. There has been an appreciable decrease in deaths from stroke, and some of this decrease may be attributable to recent advances in therapy for high blood pressure.

While the National Institute of Neurological Diseases and Stroke is primarily responsible for programs on those aspects of stroke that deal with brain injury and its consequences, the NHLI is responsible for programs on the cerebrovascular pathology that underlies stroke.*

Coronary Heart Disease

Coronary heart disease refers to the consequences of atherosclerosis in the arteries that supply the heart muscle. A heart attack is a manifestation of coronary heart disease and occurs when a coronary artery is blocked, preventing the blood from reaching the heart muscle normally nourished by the artery. This produces death of the heart muscle, technically called myocardial infarction (Figure 5). Depending upon the site of the coronary blockage, a small or a large fraction of the total heart may be involved.

Heart disease associated with arteriosclerosis of the coronary arteries remains the predominant form of heart disease in the adult American population. It is responsible for chronic illness in 4 million Americans, 2.5 million below the age of 65. In 1972, coronary heart disease accounted for about 685,000 deaths in this country. It is the largest single cause of death from cardiovascular disease and is the leading cause of death in men after age 40 and in women after age 60. Each year, approximately 170,000 persons below age 65 die of coronary heart disease.

Coronary heart disease may also result in angina pectoris (a temporary pain usually located in the center of the chest and left arm that is brought on by exercise, exposure to cold, and other factors and relieved by rest), heart failure (impaired pumping performance of the heart leading to accumulation of fluid in the body and congestion in the lungs), disturbances of heart rhythm, and sudden death.

**As of March 14, 1975, name changed to National Institute of Neurological and Communicative Disorders and Stroke.*

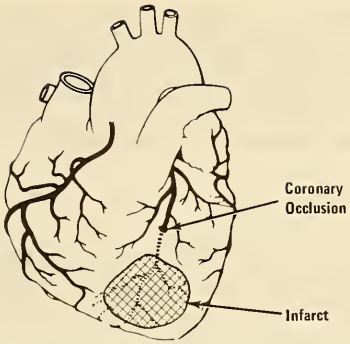


Figure 5. Schematic Diagram of Human Heart Showing Infarct
Due to Partial Blockage of Coronary Artery System

The coronary artery bypass operation has been perfected surgically and can bring increased blood supply to endangered heart muscle. This technique uses a blood vessel graft to bypass narrowed or occluded segments of coronary arteries. Over 25,000 such operations are being done annually in the United States, with hospitalization costs in excess of $5,000 for each operation. Although such surgery generally provides substantial decrease of symptoms in patients with severe angina pectoris, the long-term effects upon mortality and the clinical circumstances in which it is preferable to medical therapy are not adequately defined.

Peripheral Vascular Diseases

Peripheral vascular diseases are the cause of considerable suffering and disability. They are abnormalities that occur within arteries or veins. Atherosclerotic narrowing may result in inadequate blood flow through the arteries. The veins may become dilated (varicosities) or inflamed and obstructed by blood clots (thrombophlebitis). These diseases may be painful and result in organ damage, skin ulcerations, and gangrene. Peripheral vascular disease in the legs may affect the ability to walk or run. Thrombosis in the veins may produce pulmonary embolism, i.e., clot fragments may be carried in the blood from their site of origin to the lungs. This in turn may result in shock and death. About 265,000 patients are discharged from hospitals each year with a primary diagnosis of peripheral vascular disease.

Arrhythmias

Arrhythmias, or abnormal heart rhythms, are one of the most common manifestations of various types of heart disease and they are frequently the immediate cause of heart failure and death. Arrhythmias result from an alteration in the normal generation and transmission of electrical impulses within the heart.

They may also occur without recognizable disease. Many rhythm disturbances have minor influence upon life expectancy and cause little disability, while others cause serious symptoms, and some are almost instantaneously fatal. For example, arrhythmias kill more than half of the patients with coronary heart disease and are a major problem in patients with rheumatic heart disease. The National Program is concerned with the development of improved methods for prevention, diagnosis, and management of arrhythmias.

Heart Failure and Shock

Heart failure and shock represent major causes of death and may be the consequence of various disorders ranging from inadequate pumping by a severely damaged heart (cardiogenic shock), loss of blood (hemorrhagic shock), and impairment in the control of arterial tone. Heart failure occurs when the heart has been damaged so extensively that its ability to pump blood is impaired and it can no longer meet the needs of the body. In its chronic form, it is often associated with shortness of breath, accumulation of fluid, and swelling of the legs. Shock is also a secondary phenomenon characterized by an inability of the heart and peripheral arterial tone to maintain adequate blood pressure and blood perfusion. Left untreated, it rapidly leads to irreversible damage to such critical organs as the brain and the kidney, and ultimately to death.

Heart failure and shock are the most common causes of in-hospital deaths from heart attack and most other types of heart disease, thus accounting for about a quarter of a million deaths annually. In addition, chronic heart failure may follow a heart attack or result from high blood pressure or other cardiovascular diseases. About two million Americans have chronic heart failure. In the majority of chronic heart failure patients, symptoms can be relieved by drugs.

In the absence of valvular lesions or intracardiac defects, insufficient surviving or poorly functioning heart muscle is the immediate cause of heart failure and shock in most instances. An improved understanding of energy utilization in heart muscle is essential for adequate control or prevention of heart failure and shock in these cases.

Congenital and Rheumatic Heart Diseases

Congenital heart disease occurs when the heart or major blood vessels near the heart fail to mature normally before birth. About half of the children born with this disease do not survive until their first birthday. The causes of congenital heart disease are generally unknown. Less than three percent are known to be related to a particular event or disorder occurring during pregnancy, such as rubella (German measles), infection, or the use of certain drugs, such as thalidomide.

At present there are 35 recognizable types of congenital or inborn heart defects and about 25,000 babies are born each year with heart defects. The postnatal mortality from heart defects is about 7,500 per year. In addition, there are 100,000 children and 1,600,000 adults with known rheumatic heart disease with an annual mortality rate of about 15,000.

The earliest surgical successes in the treatment of heart diseases were in the correction or palliation of congenital heart disease. These successes are being exploited in the development of diagnostic and surgical techniques applicable to the newborn. Important insights have also been gained into the development of the cardiovascular system. However, in most cases, it is still not known what makes the heart develop abnormally before a baby is born.

Rheumatic fever and rheumatic heart disease were once considered leading causes of serious childhood illnesses. They can now be prevented. Rheumatic fever is almost always preceded by a streptococcal infection and may be prevented by prompt treatment of such infections. Rheumatic heart disease is an immunological disturbance that frequently occurs years after initial rheumatic fever and prior streptococcal infection. This type of heart disease may lead to serious damage of the heart valves. This, in turn, may not only shorten life, but also seriously impair the quality of the patient's life. Improved understanding and control of immunological problems is thus important in the identification of susceptibility and the prevention of rheumatic heart disease, as well as in the success of cardiac transplants and in the prevention of cardiomyopathies and possibly other forms of heart disease.

Cardiomyopathies and Infections of the Heart

Cardiomyopathies and infections of the heart are diseases of the heart muscle and its lining. These diseases cause enlargement of the heart, heart failure, irregularities of the heart rhythm, and occasionally sudden death. The prevalence of these diseases, caused by a variety of factors, is unknown. Known factors producing cardiomyopathies include toxic substances, viral infections, alcohol, immunological phenomena, nutritional deficiencies, muscular dystrophy, and a number of rare diseases. The condition may be acute or chronic and progressive. Rapidly fatal disease may be associated with heart failure, disturbances of rhythm, and sudden death. Infections may affect the heart muscle (myocarditis), its interior wall (endocarditis), or its exterior surface (pericarditis). They may be caused by certain viruses, bacteria, or fungi. Cardiomyopathies and myocarditis are being recognized with increasing frequency.

Circulatory Assistance

Circulatory assistance to the failing heart may be provided by many types of devices currently under development. Some are applied externally to the lower extremities in synchrony with the heart beat. In others, the pumping action of the heart is enhanced by synchronously expanding and collapsing a "balloon" positioned in the aorta, the artery leading from the heart. On a very limited scale, a few devices have been employed which require substantial surgery and the actual positioning of a pumping device within the chest. While circulatory assist devices are designed to improve the mechanical function of the heart, the apparatus also generally involves important electronic, pneumatic, hydraulic, and mechanical systems.

RESEARCH PROGRAMS

The National Heart and Lung Institute's research programs in ten major program areas are discussed individually in the following pages.

The updated National Program in each area represents an assessment and orderly expansion of the Institute's activities in response to the mandate of the National Heart, Blood Vessel, Lung, and Blood Act, and includes detection, diagnosis, treatment, and prevention programs. In the Act, the Institute is mandated to conduct research programs including investigations of the epidemiology and etiology of heart and blood vessel diseases and studies of the basic biological mechanisms and processes involved in normal and abnormal phenomena. The array of current and long-range opportunities and needs for advancement is impressive and expanding. The approaches that appear most promising, most efficient, and are most needed to develop new knowledge about heart and blood vessel diseases are summarized here.

1. ARTERIOSCLEROSIS

PROGRAM GOALS

To understand why and how arteriosclerosis develops and how to control it are two of the primary objectives of the National Program for diseases of the heart and blood vessels. Research in the recent past has clearly delineated the dimensions of the problem, has taught us much about how arteriosclerotic plaques develop, and has disclosed major risk factors such as high blood lipids, high blood pressure, heavy cigarette smoking, and others that particularly predispose to arteriosclerotic disease. Yet the way in which these factors operate to promote arteriosclerosis remains obscure. The current information on the atherosclerosis process is inadequate to develop methods to control the disease by altering lesion development.

Clearly, the prevention or control of arteriosclerosis, even to a limited extent, would be far better for our quality of life and far less costly than are the medical treatment and the social accommodations of the consequences of manifest disease, such as heart attacks, strokes, and deaths. There now exist meaningful leads both at the fundamental and applied levels of knowledge that can be pursued. On the one hand, therefore, the Institute proposes to continue to give emphasis to the conduct of clinical trials to determine the efficacy of promising current preventive or control measures. On the other hand, it will continue to seek new information about the fundamental development and causes of arteriosclerosis and thus seek to provide the means for its prevention.

- The primary goal in arteriosclerosis is prevention. To do this we must gain a better understanding of its basic processes, and improve the diagnosis and treatment of the process and its sequelae.

PROGRAM STATUS

Recent Progress. The attack on arteriosclerosis extends across many fundamental disciplines and a wide spectrum of activities ranging from metabolic studies, clinical investigations and preventive trials, pathology, epidemiology, clinical medicine, and others. Some examples of recent progress resulting from this work are given below.

It is known that disorders and elevation of blood fats enhance arteriosclerosis, and a major research effort is going on in this area. The NHLI Lipid Research Clinics, a program involving twelve clinics, a coordinating Center, an electrocardiographic center, and a central laboratory, have succeeded in standardizing automated methods for the diagnostic analysis of cholesterol and triglycerides and of diagnostic lipoprotein typing. This information has been made available as an educational resource manual. It will greatly improve the availability and accuracy of such diagnoses. The prevalence of lipid disorders has been under study for two years at eleven of the clinics. This data is almost complete and is under analysis. It will provide for the first time a clear picture of the frequency of different kinds of lipid disorders. The international significance of such data is being ascertained through one clinic in Canada and through extension of some of the studies to two clinics in the Soviet Union, developed under the US-USSR cooperative program in health. A protocol or plan to study genetic aspects of lipid disorders in families has been developed, as has one which will determine the significance of the detection of lipid disorders in fetal cord blood at birth.

Because cholesterol and fat in the diet are known to influence blood fats, detailed dietary records are being obtained using improved recall questionnaires developed jointly by the Lipid Research Clinics and in the Multiple Risk Factor Intervention Trial (see below). A central computerized data system has been created to evaluate the role of diet in hyperlipidemia and the association of diet with the incidence of cardiovascular disease.

One of the most severely atherogenic lipid disorders is Type II hyperlipoproteinemia. Patients with this disorder have a high incidence of premature coronary heart disease. In certain patients in whom both parents have the disease (homozygous Type II patients), heart attacks occur before the age of 10. The blood cholesterol of Type II subjects can be lowered somewhat by therapeutic diets and to a greater degree by a combination of diet and a cholesterol lowering drug, cholestyramine. From the populations under study by the Lipid Research Clinics, about

4,000 male volunteers with Type II hyperlipoproteinemia are now being recruited for a controlled therapeutic trial to determine whether lowering of blood lipid levels will prevent or delay heart disease. By the end of 1974, 500 patients had been randomized into the study.

The Clinics act as educational resources about disorders of lipid metabolism, their diagnosis and treatment, and for nutritional information. Because of this and because of recruitment and adherence needs of the Type II intervention trial noted above, the Clinics have begun to utilize expert guidance and to initiate research in the behavioral, educational, and media communication fields. An interdisciplinary group of behavioral scientists, cardiologists, nutritionists, and psychologists is studying health attitudes, preferred modes of learning, and the communication media best suited to educate the public generally, various types of health professionals, as well as the patients involved in the trials.

Related to the same goals as those of the Lipid Research Clinics, but with more emphasis on the fundamental manner of development and early manifestations of arteriosclerosis, are the research programs of the Specialized Centers of Research and of the Institute's own intramural scientists. Progress has been made in ascertaining the prevalence of adult-type risk factors (high blood pressure, high blood cholesterol) for arteriosclerotic disease in children. Approximately 12,000 children have now completed two years of a four-year longitudinal study of blood pressure and of blood cholesterol. Studies of lipids, hypertension, and of heart disease have been initiated in the families of some of the children. Such studies may help to clarify whether arteriosclerosis is to be regarded as a disease of childhood rather than one of young adult life.

There are extensive studies going on of the structure, function, and metabolism of lipoproteins, the form in which fats and cholesterol are transported in the blood. This work has identified the metabolic rate and structural sequence of several lipoprotein proteins and has elaborated the roles of the lipoprotein lipase enzymes in their metabolism of the intact lipoproteins. The ability of specific lipoprotein proteins to bind or carry lipids is under active study.

Diet, and particularly its content of certain fats and cholesterol, influence both the concentration and composition of blood lipids in the body. The relationship of nutritional factors to lipid metabolism and development of atherosclerosis is being studied. The ongoing cooperative effort to update the nutrient composition and source book used in this study continues. (See section on Program Coordination.)

Several investigators are seeking to improve the diagnosis of arteriosclerotic plaques in vessels. A computerized method of reading angiograms has been developed as have sophisticated methods of visualizing blood flow in selected vessels. In addition, the sound emitted as blood flows through arteries narrowed by arteriosclerosis has been utilized to improve the diagnosis of vascular disease. Studies continue in search of a satisfactory method for the noninvasive diagnosis of arteriosclerosis.

Basic research on the development of the arteriosclerotic plaque in the artery wall itself continues. There has been some clarification of the role of local cellular multiplication in the buildup of plaques, the flux of lipids in plaques, their entry into the intima through damaged or normal endothelium, the function of endothelium, and the production of plaque substance between cells. Extensive studies of the regression of experimental arteriosclerosis that will average three or four years in duration are approximately halfway through their course. The results of these studies should indicate the level of hypercholesterolemia at which regression may be expected.

The processes leading to atherosclerosis are closely related to altered permeability of the arterial wall. In atherosclerosis, lipids are deposited in the wall more rapidly than they are removed. Fats such as cholesterol are transported in the blood as lipoproteins. Very recent studies indicate that in familial Type II hyperlipoproteinemia a defect in lipoprotein clearance at a cell membrane receptor site is fundamental to the process. These studies provide further molecular definition of a familial disorder associated with cardiovascular disease.

Studies on the transport of lipids to and from the arterial wall have been extended by the development of better techniques of isotopically labeling lipid and protein components of plasma lipoproteins to permit analyses of the transport mechanism of these molecules into the arterial wall. Methods to determine alterations in the "chemical barrier" and wall ultrastructure have also been developed.

The process of lipolysis is central to the utilization of lipids by the body, and is a major determinant of blood lipid levels. The part played by various enzymes in the arterial wall during this process is being explored. Lipoprotein lipases--the principal enzymes in this process--have been the subject of intensive study almost continuously since their discovery at the NHLI 20 years ago. There are at least two different lipases that can be liberated into blood to hasten lipid removal. Lipoprotein lipase is selectively absent in familial Type I hyperlipoproteinemia and this leads to abnormal levels of lipid in the blood. Previous

observations on the rapid and reversible effect of insulin on lipids have been further advanced and it is now possible to study more directly the effects of insulin and adrenal hormones in the handling of lipids.

Two extensive studies of patients with Type II hyperlipoproteinemia have been completed. One study analyzed over 200 children born of parents with a form of familial Type II hypercholesterolemia. The genetic data indicate a clear-cut mode of inheritance determined by a single gene and the hyperlipoproteinemia is manifested early in childhood. The companion analysis of over 1,000 relatives of affected patients is the most extensive such analysis ever undertaken of this genetic defect. This study provides striking evidence of the premature atherosclerotic risk of patients affected with this disorder.

A major study has begun of the prevention of initial heart attacks among men at high risk because of elevated blood cholesterol, high blood pressure, and cigarette smoking. This primary prevention trial, called the Multiple Risk Factor Intervention Trial (MRFIT) will seek to revert these risk factors toward normal and to ascertain if this intervention has an effect on the incidence of heart attacks. This trial is particularly important because it seeks to prevent first heart attacks and to do so among that segment of the population at highest risk. It will also produce practical information on how best to accomplish risk reduction. At the present time some 20 clinics, a coordinating center, and a central electrocardiographic and chemistry laboratory have become participants in the study, the protocol has been designed, and recruitment and screening of subjects has begun. By the end of 1974 more than 150,000 men had been screened for coronary heart disease risk factors, and 5,196 of these subjects with higher than average risk have been enrolled in this planned six-year intervention trial.

A study is in progress of cardiovascular risk factors and the familial and genetic associations of offspring of 1,644 spouse sets who were part of the original Framingham Study. In addition, extensive data have been collected on more than 600 twin pairs in an NHLI study. Preliminary results from this twin study indicate that there are genetic determinants of the observed variability in height, weight, and blood pressure. A similar study is also in progress of the offspring of the Honolulu participants in a Honolulu-Hiroshima-San Francisco Heart Disease Study.

In 1974 the first National Research and Demonstration Center in Cardiovascular Disease was established. This Center is largely devoted to arteriosclerotic disease. It is multifaceted and includes basic research, clinical investigation, development of programs of education, and community demonstrations. It represents a cohesive, unified approach to the goals outlined earlier.

Future Challenges. Our present understanding of the fundamental nature and processes of arteriosclerosis must be improved before specific approaches to prevention can be developed. If highly specific preventive measures or therapy are to become available, a broad research program to clarify the pathogenesis of this disorder is essential.

Practical understanding and control of arteriosclerosis is constrained by lack of good noninvasive diagnostic methods, by lack of understanding of the fundamental processes by which arteriosclerosis develops, by uncertainty about the efficacy of control measures, and by the need for effective means of health education and health behavior communication. Each of these broad areas provides major opportunities and challenges.

The present state of technology suggests that the development of superior, more effective and convenient diagnostic instruments is possible. Advances are being made with ultrasound, densitometric methods, pulse wave interpretation, and computer assisted image and signal processing. Further progress is needed to provide easier and more accurate methods of diagnosis.

Many fundamental processes involved in arteriosclerosis cannot be studied in man or are better studied in experimental animal models of human disease. There is lack of convenient access to animal models of chronic disease, particularly nonhuman primate models, which closely mimic human disease. Also, the supply of wild nonhuman primates for use by investigators has become restricted. Genetic metabolic disorders of lipid metabolism and of hypertension exist in animals and these permit both metabolic and genetic studies impossible to carry out in man. There is an opportunity for the Institute to facilitate the supply of animal models.

There are indications that some lipid disorders, hyperlipoproteinemia, and also the inherent susceptibility to arteriosclerosis have a genetic component in man. However, the genetic influence is complex and not well understood. Populations currently under study by the Institute for other reasons may provide an unusual resource to elucidate these genetic influences.

The evaluation of preventive measures for coronary heart disease continues to be an important challenge. Several trials are underway or in the initial recruitment and start-up stages. Their duration will extend several years into the future and their findings will do much to condition medical and public health attitudes to the prevention of diseases related to arteriosclerosis.

PROGRAM PLANS

Actions. The Institute plans to:

- Emphasize pathogenetic studies within existing and new research programs, centers of research, and lipid research clinics

- Stimulate further development of sensitive, specific, invasive, and noninvasive diagnostic techniques to determine arteriosclerotic changes in blood vessels

- Evaluate current techniques for diagnosis of hyperlipoproteinemia and other risk factors and encourage the development of better ones

- Establish colonies of suitable animal models, particularly nonhuman primates, with arteriosclerotic or hypertensive disease for use in research on arteriosclerosis, hypertension, and cerebral vascular disease, and encourage animal research in genetic defects related to arteriosclerosis

- Expand current population studies to include in-depth genetic studies in the Institute's Lipid Research Clinics, Specialized Centers of Research in Arteriosclerosis, and Clinical Application and Prevention programs

- Continue the newly implemented Multiple Risk Factor Intervention Trial (MRFIT) to determine whether, for men at above average risk of death from coronary heart disease (because of elevated serum cholesterol, elevated diastolic blood pressure, and cigarette smoking), a special intervention program will result in a significant reduction in mortality from coronary heart disease

- Continue an intervention study in high-risk subjects (Type II Primary Prevention Trial) to test whether lowering the concentration of lipids by selected means reduces cardiovascular mortality and morbidity

- Provide for acquisition, analysis, and storage of data on the prevalence of different types of hyperlipoproteinemia, particularly in young age groups, with special emphasis on their relationship to diet and premature atherosclerosis

- Promote further clinical, laboratory, and epidemiologic studies of personal attributes and life styles such as nutrition, exercise, obesity, diabetes, cigarette

smoking, behavior, biochemical and hormonal patterns, and response to psychosocial stress and their relationship to the development of arteriosclerosis, coronary heart disease, stroke, and hypertension, particularly with respect to the onset of arteriosclerosis in the young and in women

- Expand current population studies and develop new epidemiologic studies of the role of environmental factors such as trace substances, water hardness, climate, geography, and occupational exposures, in the pathogenesis of arteriosclerosis

- Continue the US-USSR cooperative study to define the prevalence of different types of hyperlipoproteinemia, their relationship to environmental factors, especially nutrition, and other broadly defined cardiovascular risk factors.

Schedule. The costs of clinical trials now in progress will plateau in FY 76. Present programs dealing with the prevalence of lipid abnormalities and hypertension in children and adults will be completed between FY 76 and FY 78. An enhanced program of diagnostic instrument development will be initiated in FY 75 and is projected for 5 years. A series of animal model resources is to be initiated in FY 75. These resources are projected for at least 5 years and may be required for longer. The initial steps have been taken to stimulate research in genetic and psychosocial and behavioral studies. These will be consolidated in FY 75 leading to new programs in FY 76.

2. HYPERTENSION

PROGRAM GOALS

In the great majority of cases we currently lack the means to prevent or cure hypertension even though treatment is possible. The serious nature of hypertension, the vast numbers of persons affected, and the logistical, medical, and motivational problems associated with its treatment make it essential that enough understanding be gained through research to allow its prevention or cure. At the same time, effective treatment currently exists and its use should be enhanced.

- Major long-term goals in hypertension are to understand its causes and to reduce its prevalence

- An immediate goal is to optimize the use of currently available effective treatments.

PROGRAM STATUS

Recent Progress. Hypertension is a condition resulting from a breakdown in the complex control system that maintains equilibrium between the constricting and the dilating forces of the arterial walls and the forces of the circulation. In hypertension, the normal level of balance is shifted upward so that the blood is circulated in the arteries under higher pressure. The increased pressure may damage both the blood vessels and the heart. The roles of the several vasodilating and vasoconstricting systems in the control of normal and elevated blood pressure are currently under intensive investigation.

The kallikrein-kinin system may play an important role both in blood pressure regulation and in kidney function. Kallikreins are enzymes found in the kidney, urine, blood, and various exocrine glands. Kallikreins regulate the production in the blood of kinins, the most powerful blood vessel dilators known. Studies have shown that the excretion of urinary kallikreins is abnormally low in essential hypertension. Thus, determinations of the level of urinary kallikreins may help to distinguish between essential hypertension and elevated blood pressure secondary to excessive secretion of aldosterone (due to tumors or other pathological conditions affecting the adrenal glands). Urinary kallikrein levels are abnormally high in patients with primary aldosteronism, whereas it is low in those with essential hypertension.

The renin-angiotensin-aldosterone vasoconstrictor system and its role in hypertension have been under intensive study. Recently improvements in assay procedures have greatly facilitated the interpretation of research findings in this area. Another humoral system that may possibly be implicated in hypertension involves prostaglandins, and further studies are underway to determine their role.

Research indicates that blood pressure, the output of various hormones and vasoactive substances, and the urinary excretion of sodium and potassium rise and fall rhythmically in cycles lasting approximately 24 hours (circadian rhythms). These rhythms vary from individual to individual and are subject to modification by such factors as changes in diet (especially sodium intake), stress, sleep-wake schedules, and geographical displacement such as occurs when an individual flies nonstop across several time zones. Fuller understanding of circadian rhythms in hypertensive patients may help in the selection of the most suitable agent for blood pressure control and also the optimal time of day to take it. For example, thiazide diuretics, which promote sodium excretion by the kidneys, are often used in the treatment of hypertension; but thiazides may also produce unwanted potassium deficits. Recent studies in hypertensive subjects taking thiazides at various times showed that these agents produced maximal sodium excretion with minimal potassium losses when administered at 8 a.m. each day.

The past year has seen the further development of work on factors that may be involved in hypertension. Much of this work has been conducted within the Specialized Centers of Research for Hypertension which are devoted to multidisciplinary research in high blood pressure. A solicitation for additional Centers was issued this year, and applications will be reviewed for funding in FY 76. A major international conference on the kallikrein-kinin system was held this year, as was the Second International Symposium on Hypertension.

It has been recognized that there is a need to standardize and maintain certain genetic strains of rats with hypertension and rats prone to stroke. Steps have now been taken to assure a proper supply of such animals for research. The Institute of Laboratory Animal Resources (part of the National Academy of Sciences) has been awarded a contract to prepare a monograph on the care and use of a genetic strain of rats that are spontaneously hypertensive. The Institute has also arranged for NIH's Division of Research Services to establish and maintain a colony of stroke-prone rats (a subgroup of the spontaneously hypertensive rats). Nonhuman primate models of chronic hypertension will be initiated and will be brought under study. (See earlier section on Arteriosclerosis.)

In 1973 a major cooperative community-based clinical trial, the Hypertension Detection and Follow-Up Program, was started. Cross sections of ethnic and racial groups and of socioeconomic strata in 14 communities are being studied for prevalence of all ranges of hypertension. The effectiveness of treatment in reducing morbidity and mortality of all ranges of hypertension is being evaluated. The past year has seen the completion of screening of approximately 160,000 persons; 23,000 were found to have some degree of hypertension at the first examination. The goal to enroll at least 10,500 individuals in a controlled study has now been attained. An important component of this study relates to health education and behavioral research as these may affect adherence to therapy and personal attitude towards hypertension.

In cooperation with the Veterans Administration (VA), a related study has enrolled subjects and begun to test the efficacy of treatment of mild hypertension. A retrospective study of the incidence and course of hypertension from early childhood to middle age was also initiated by the Institute during the year.

Future Challenges. The major research challenge is to discover the causes of hypertension so as to have a rational basis for prevention. Present knowledge, although it allows treatment, does not enable prevention or cure for the great majority of cases.

There is need to ascertain the value of treating mild hypertension. Approximately four-fifths of those with hypertension have this milder condition. Therefore, it is important to learn if and to what degree treatment may be necessary. Moreover, while effective drugs do exist, improved therapies that would simplify treatment, avoid side effects, and be more economical are needed.

Dissemination of information about hypertension to the public and to the health care community continues to be a challenging task. It is discussed further in the section on Prevention, Control, and Education.

PROGRAM PLANS

Actions. The Institute plans to:

- Emphasize research on the etiology and pathogenesis of hypertension, including its epidemiology
- Implement clinical trials of antihypertensive therapy in mild and labile hypertension
- Evaluate new pharmacologic approaches to the treatment of hypertension with emphasis on new drug formulations
- Continue the Hypertension Detection and Follow-up Program (HDFP), a cooperative clinical trial to determine the effectiveness of intensive antihypertensive therapy in reducing morbidity and mortality from hypertension in general community populations.

Schedule. Present programs will continue to receive emphasis. The HDFP will complete the first cycle of annual home follow-up blood pressure measurements on the entire randomized population enrolled in the study. Monthly monitoring of the data and progress of the study will continue. The prevalence studies of hypertension in children will be completed (see section on Arteriosclerosis). Continuing and new actions will increase somewhat in FY 75 and increase further by FY 80. Part of this increase is attributable to the proposed clinical trial of therapy for mild hypertension. Additional increases will occur in studies of the pathogenesis and pharmacology of hypertension. Proposals for new multidisciplinary Specialized Centers of Research in Hypertension will be reviewed this year but are not likely to begin activity until early FY 76.

3. CEREBROVASCULAR DISEASE

PROGRAM GOALS

Cerebrovascular disease due primarily to arteriosclerosis and to hypertension is the basis for the great majority of strokes. The

National Institute of Neurological Diseases and Stroke* is primarily responsible for programs on those aspects of stroke that deal with brain injury and its consequences, whereas the National Heart and Lung Institute is responsible for programs on the cerebrovascular pathology that underlies stroke.

- The goal of the program is to decrease the incidence of stroke through studies of the pathology and pathogenesis of cerebrovascular disease.

PROGRAM STATUS

Recent Progress. The National Heart and Lung Institute collaborates with the National Institute of Neurological Diseases and Stroke* in a joint council subcommittee on cerebrovascular disease.

Currently there are a variety of studies on measurements of cerebral blood flow and its control. However, relatively few investigations deal with the problems of the etiology and pathogenesis of cerebrovascular lesions in man or in animals.

The Institute has initiated chronic modeling of arteriosclerosis and of hypertension in nonhuman primates to be used in the study of cerebrovascular disease leading to stroke. (See Arteriosclerosis section.) In addition, with the cooperation of the Division of Research Services (NIH), a resource colony of stroke-prone rats has been established. These rats will allow studies of the relation of hypertension to stroke (see Hypertension section).

Future Challenges. To determine the etiology and prevention of stroke, animal studies need to be conducted to monitor the effects of chronic arteriosclerosis and chronic hypertension on the arteries of the brain. As yet, little knowledge is available about chronic vascular changes in animal models, particularly in nonhuman primates which are appropriate for neurological examination. The aim of these animal studies is to elucidate, by methods not applicable to man, the vascular pathology that leads to stroke. Cerebrovascular disease is closely related to arteriosclerosis and hypertension. Therefore, the future challenges discussed in the sections on Arteriosclerosis and Hypertension also apply to Cerebrovascular Disease.

PROGRAM PLANS

Actions. The Institute plans to:

- Initiate animal studies of the pathology of the lesions of chronic atherosclerosis and hypertension in the cerebrovascular arteries, emphasizing studies of lesions that

*As of March 14, 1975, name changed to National Institute of Neurological and Communicative Disorders and Stroke.

may contribute to ischemic stroke or arterial brain hemorrhage; and utilize, with minor expansion or redirection appropriate to the study of cerebrovascular disease, the chronic and serial animal resources referred to in the sections on Arteriosclerosis and Hypertension

- Continue prospective epidemiologic studies dealing with the identification of environmental factors and personal attributes which predispose to increased risks of stroke; and maintain surveillance of stroke end-points in the clinical trials discussed in the sections on Arteriosclerosis and Hypertension.

Schedule. The development of animal resources has been initiated. The planned actions in animal studies and clinical research will gradually increase the current program effort in the cerebrovascular area through FY 79.

4. CORONARY HEART DISEASE

PROGRAM GOALS

Coronary heart disease is by far the most frequent complication of arteriosclerosis. Improved understanding of the onset, causes of heart malfunction, mode of death, and corrective procedures could have a substantial effect in reducing the exceedingly high morbidity and mortality from coronary heart disease. A major goal is to acquire knowledge about coronary heart disease both in the basic science laboratories and in clinical areas. Such research will provide further understanding of how the heart responds to periods of decreased blood flow, how it can be protected during such periods, how the patient responds to coronary disease, and the value of various forms of treatment.

- A major goal of the program is to develop information that will lead to improved diagnosis, prevention, therapy, rehabilitation, and understanding of the mechanisms resulting in symptomatic coronary disease.

Coronary bypass is a surgical means of treating severe coronary heart disease by routing blood around the obstructions in diseased coronary arteries. This technique brings increased blood supply to endangered heart muscle. Early results with this operation are encouraging, and relief of symptoms has been demonstrated. Whether symptomatic relief persists over the years and whether the procedure reduces the risk of heart attacks and improves long-term survival remain to be determined.

- A second goal is to establish the indications for the effectiveness of coronary artery surgery in the treatment of various forms of coronary heart disease.

Each year about 400,000 deaths from coronary heart disease occur before hospitalization, half of these almost instantaneously or unwitnessed. Over three-quarters of these victims have known coronary artery disease or high blood pressure before their sudden deaths, but, in the rest, sudden cardiac death is the first evidence of heart disease.

- A third goal is to develop and assess emergency medical care methods for heart attack victims and to develop and evaluate prophylactic treatment with drugs to prevent sudden cardiac death.

Following heart attack or other manifestation of heart disease, tens of thousands of Americans annually are left with substantial impairment of their ability to function and to contribute to society. Thus, one aspect of the National Program in coronary heart disease deals with the development of improved methods of rehabilitation.

- A fourth major goal of the program is to assess the needs and opportunities for cardiac rehabilitation with respect to physical, psychological, and societal factors to prevent disability and to bring back into the mainstream of life those who have suffered cardiovascular disease.

The survivors of heart attacks are particularly prone to a recurrence, and there is a need for measures to prevent these recurrent attacks.

- A fifth major goal of the program is to assess drug therapy for the prevention of recurrent heart attack.

In addition to the topics identified under coronary heart disease, relevant work on the primary prevention of heart disease is described in the section on Arteriosclerosis. Other relevant research is described in the sections on Arrhythmias, Heart Failure and Shock, and in the section on Prevention, Control, and Education.

PROGRAM STATUS

Recent Progress. Proposals for Specialized Centers of Research to conduct investigations on the various manifestations of coronary heart disease have been reviewed, and these centers will begin operation in FY 75. Phase I of the Collaborative National Study on Coronary Artery Surgery is completed and collection of the data necessary to plan the definitive randomized studies and registry is underway. The US-USSR Cooperative Study on Management of Ischemic Heart Disease is proceeding on schedule. The results of present studies on mechanisms and factors precipitating acute cardiovascular events and their prodromata have been presented at a national conference. Pilot testing of antiarrhythmic drugs administered to patients following hospitalization for acute myocardial infarction is near completion and plans for definitive trials are being developed. A task force has reported on the needs and opportunities for the physiological, psychological, and societal rehabilitation of patients with cardiovascular disease.

An earlier goal of the program on coronary heart disease was the in-depth characterization of patients with acute myocardial infarction. Data banks with extensive, readily retrievable information on large numbers of patients have been established. These data are now being used to plan patient management and as a resource for designing clinical trials. Patient information is being extended to include long-term follow-up, and the data base is being expanded to include patients with coronary heart disease without acute infarction. With the advent of coronary artery surgery and coronary arteriography these data banks have taken on a new dimension. Information is now available on the relationships between coronary artery lesions and heart disease. These data show that between 10 to 20 percent of typical clinical coronary heart disease (angina pectoris, acute myocardial infarction) is not associated with substantial coronary artery disease, whereas, even more frequently, severe diffuse coronary artery disease is not associated with significant clinical heart disease. Studies have shown that coronary atherosclerosis, which was until recently considered a relentless progressive process, may be very stable. On the other hand, coronary artery spasm, once considered relatively rare, is frequently observed and may be a relatively common cause of acute symptoms. A randomized medical/surgical trial of unstable angina pectoris patients (patients believed to be prone to acute infarction) is near completion. The results of this trial should have a major impact on present modes of therapy.

A more complete characterization of the sudden cardiac death syndrome is now available. A collaborative study of retrospective histories and detailed post mortem examinations has been completed as well as a study correlating multiphasic screening in a prepaid health plan with subsequent sudden death. Data on the acute event have been obtained from rescue operations, stadia, and emergency rooms. In terminal patients for whom records were available,

80 to 85 percent do have significant coronary artery disease, and their history up to the acute terminal episode does not appear to differ significantly from other patients with coronary heart disease. Although prompt treatment of individual acute episodes in a relatively small series of patients is impressive, the overall success rate with present measures has a limited impact upon general mortality.

The Coronary Drug Project, one of the major clinical trials to assess the possible efficacy of several blood lipid-lowering agents in reducing the incidence of recurring myocardial infarction, is now completed. This study was conducted in 8,400 men, age 30-64, with one or more heart attacks prior to entry into the study. The trial has uncovered unfavorable features of estrogen and dextrothyroxine, two of the drugs once considered potentially beneficial for these patients. This information has been communicated to the medical community. Additional results from this double blind study have been discussed in the "Highlights" section of this report.

Pilot studies have been successfully undertaken for a large-scale clinical trial to determine whether the ingestion of aspirin reduces the incidence of recurrent myocardial infarction. A definitive trial is being implemented.

Diagnosis and treatment of both acute myocardial infarction and complications of chronic coronary heart disease have advanced greatly in the recent past and these are described in more detail in the sections on Arrhythmias and on Heart Failure and Shock.

Future Challenges. The emphasis in patient-oriented research is shifting from its current focus on the acute heart attack to other important aspects of coronary heart disease, such as angina pectoris and early arrhythmias, where prevention of future heart failure and/or death is possible. Further development and evaluation of therapy, rehabilitation, and of electrophysiological measurements are required. The fundamental question of what converts chronic coronary artery disease into acute heart disease must be answered. The study of patients susceptible to acute heart disease requires specialized facilities that are complex, expensive, and that are staffed with personnel available for emergencies. Importantly, such specialized cardiological facilities will be very useful for research on other forms of heart disease as well.

It is widely recognized that coronary artery surgery brings relief of symptoms for a majority of patients with severe angina pectoris. However, the benefits, side effects, and the effects upon life span and quality of life after surgery compared to conventional drug therapy require further research.

Recent studies have shown that the final step in sudden cardiac death is usually ventricular fibrillation. Therefore, finding drugs to prevent ventricular fibrillation in high-risk patients is an important research task. Agents must be found that can be used immediately upon the development of heart attack symptoms.

The high frequency of out-of-hospital deaths compared with the favorable experience with improved systems of emergency cardiac care underscores the need for further development of emergency-related techniques and resources for use in cardiac patients.

The promising results of early trials of aspirin on myocardial infarction and its sequelae dictate a need for a large-scale study to assess the efficacy of this therapeutic regimen.

Strengthened scientific bases for rehabilitation programs are needed as well as a more comprehensive scope of action for these programs.

Development and testing of new hypotheses and methods are critical to continued clinical and fundamental research into the cause, diagnosis, and treatment of coronary heart disease.

PROGRAM PLANS

Actions. The Institute plans to:

- Establish approximately ten specialized units to conduct research on the various manifestations of coronary heart disease. Comprehensive clinical investigations will be supported by related, fundamental laboratory studies.

- Continue and enlarge a collaborative national program to determine the indications for and the long-term effects of coronary artery surgery in the management of coronary heart disease. Randomized studies will be utilized in patients with sharply defined clinical conditions and coronary arterial involvement. A registry will be used to follow patients in whom the indications for surgery or exclusively medical treatment seem sufficiently clear that randomized allocation would be improper, but in whom follow-up clinical data are important to assess the validity of present clinical judgments.

- Continue the US-USSR cooperative study on the management of ischemic heart disease by medical and surgical techniques.

- Promote studies to elucidate the mechanisms and factors which precipitate acute coronary events and to determine the characteristics of individuals at highest risk for these events.

- Promote studies on the prodromata of acute coronary events and of patients' reactions and coping behavior in this setting to enable earlier diagnosis and treatment.

- Develop and test techniques of emergency cardiovascular diagnosis and therapy suitable for incorporation into emergency medical care systems.

- Design and prepare for implementation of large-scale trials of chronically administered antiarrhythmic drugs in patients at high risk of sudden cardiac death.

- Continue to implement the US-USSR cooperative program on the prevention of sudden cardiac death.

- Stimulate research on cardiac rehabilitation.

- Implement a large-scale clinical trial to assess the possible efficacy of regular aspirin ingestion in decreasing the incidence of recurrent myocardial infarction.

Schedule. The Myocardial Infarction Research Units, which focused on acute heart attacks, will be discontinued in FY 75. Continuing and new actions in coronary heart disease will include a broader spectrum of chronic coronary heart disease and will cover such clinical entities as angina pectoris and sudden cardiac death. In part, this will be accomplished through the development of specialized cardiac units. Electrophysiological and surgical investigations, with specific attention to prevention of acute events, will also be emphasized.

In the coming year, targeted efforts will include a solicitation of research on sudden cardiac death and the onset of myocardial infarction and research on methods of quantifying infarct size. These represent competitive solicitations for the ongoing overall programs on these topics. There may be solicitations to increase the number of participating units in the collaborative studies on coronary artery surgery, and there will be a solicitation in the area of cardiac rehabilitation, probably starting with the development of baseline data on current attitudes regarding rehabilitation. For other topics closely related to coronary heart disease, see sections on Arrhythmias and Heart Failure and Shock.

5. PERIPHERAL VASCULAR DISEASES

PROGRAM GOALS

Peripheral vascular diseases cause considerable suffering and disability. Techniques have been developed to replace or bypass diseased arteries with vascular or prosthetic grafts. Otherwise, peripheral arterial disease, peripheral venous disease, and disorders of the lymphatics have been the focus of only a limited research effort in the past.

- The goals of this program are to improve diagnosis, therapy, and rehabilitation, and to improve understanding of the mechanisms causing peripheral arterial, venous, and lymphatic diseases.

PROGRAM STATUS

Recent Progress. Recent progress in peripheral vascular disease has centered mainly on various causes and indicators of venous thrombosis and the diagnosis and surgical therapy of arterial and venous disease. Early and sensitive indicators of thrombosis have been developed. Epidemiological aspects of venous disease and subsequent emboli have been correlated with oral contraceptives as well as with other agents and diseases. Other major advances have occurred in techniques to diagnose pathologic changes in peripheral vessels, in the evaluation of their natural history, and in the development of new corrective interventions which have been primarily surgical. The clinical diagnosis of peripheral vascular disease can now be made quite accurately with new ultrasound, radioisotope, and radiographic techniques. The ability to replace or bypass irreversibly obstructed lesions in large major vessels and medium-sized peripheral arteries has advanced markedly.

Future Challenges. Better methods must be developed for early diagnosis of peripheral vascular diseases for more effective medical management, and for the extension of surgical therapy to small vessels. Understanding the basic cause of the disease is most important. This requires further study of the role of neural control of vascular tone, mechanisms of action of smooth muscle, pathogenesis of peripheral atherosclerosis, and the importance and significance of risk factors.

PROGRAM PLANS

Actions. The Institute plans to:

- Further encourage clinical, laboratory, and epidemiological research into the causes, diagnosis, and treatment of diseases of the peripheral arteries, veins, and lymphatics

- Implement related programs described in the section on Arteriosclerosis.

Schedule. Continuing and new actions in peripheral vascular diseases will emphasize basic and clinical investigation. Emphasis will be on diagnostic techniques and the relation of physiology and pathophysiology to clinical manifestations of disease. Multidisciplinary approaches will include pathology, surgery, thrombology, disorders of hemostasis, peripheral vascular physiology and its neural control, as well as clinical cardiology.

6. ARRHYTHMIAS

PROGRAM GOALS

Arrhythmias and other electrical disturbances of the heart cause important symptoms and aggravate many forms of heart disease. They are frequently the immediate cause of heart failure and death. Identification of arrhythmias that carry a high risk of sudden cardiac death is fundamental for the development of preventive measures.

- A major goal is to develop and evaluate methods for understanding and preventing arrhythmias, particularly those which may cause sudden death.

The analysis of normal and abnormal cardiac rhythms and the influence of drugs on these rhythms must be assessed by quantitative analysis of extensive electrocardiographic recordings. Progress has been made toward performing this task automatically, rapidly, and quantitatively by computer. Further efforts are being made utilizing these methods.

- Another goal of the program is to continue to improve currently available methods for prevention, diagnosis, and management of arrhythmias and other electrical disturbances of the heart.

PROGRAM STATUS

Recent Progress. A new understanding of electrophysiological mechanisms underlying severe arrhythmias has been developed. One major advance based on pioneering studies in the 1960's has been the characterization of the slow inward depolarizing current during the prolonged plateau phase of the cardiac action potential. Recognition of the potential role of this slow inward calcium current in the genesis of lethal arrhythmias has added

a new dimension to their understanding. Agents which can influence these currents are being evaluated and may lead to the eventual control of serious rhythm abnormalities.

Another major advance has been the further improvement of computerized arrhythmia analysis systems. After many years in the developmental stage, the automated analysis of arrhythmias, both in the Coronary Care Unit (CCU) and in ambulatory patients, is now available for clinical research and patient care. Reliable extended analyses of heart rhythms can now be used to monitor the effects of chronic drug administration, the results of surgery, and occurrence of various arrhythmias in patients with and without clinical heart disease. Such analyses are an essential part of the clinical evaluation of new antiarrhythmic agents for long-term, chronic use. The end point of the evaluation is a change in mortality. These agents include quinidine and possibly propranolol which are currently at the pilot study stage. These new agents, which comprise a series of compounds with a variety of basic mechanisms of action, represent a much needed addition to the limited group of compounds which can presently be used in the clinical control of arrhythmias. Recent studies have shown that many of the agents now accepted for clinical use have limited effectiveness in many conditions and have serious side effects when administered on a chronic basis.

Future Challenges. A better understanding of the electrical behavior of the diseased heart is essential. Several drugs, effective in the coronary care unit, need to be evaluated for benefits and side effects as prophylactic agents outside the hospital in patients suspected of having myocardial infarction. Particular attention needs to be paid to the effect of heart rate upon automaticity and rhythm disturbances as well as upon the work load and consequent potential damage to the heart. Safe oral antiarrhythmic drugs for chronic administration need to be developed and evaluated. For use in these clinical studies improved systems need to be developed to quantify electrocardiographic rhythm signals automatically and rapidly. Disturbances of the conduction system of the heart, and other important rhythm disturbances, must be managed more effectively. Closely related topics are also discussed under the section on Coronary Heart Disease.

PROGRAM PLANS

Actions. The Institute plans to:

- Expand current studies on the prevention of arrhythmias. Studies will focus on the electrophysiology and therapy of rhythm disturbances associated with inadequate blood supply to heart muscle and on clinical studies to identify chronic or intermittent disturbances of heart rhythm which indicate an increased risk of sudden death.

- Augment the development of automated, quantitative techniques to analyze electrocardiographic rhythm signals to facilitate clinical investigation of arrhythmias.

Schedule. A new expanded program on arrhythmias will emphasize those arrhythmias suspected of causing sudden cardiac death. There will be an overall expansion of program activity with a peak in currently projected programs in FY 79 and FY 80, and subsequent leveling off of activity by FY 81.

In the coming year, further targeted efforts are planned in research on the control of lethal arrhythmias associated with ischemic heart disease. It is anticipated that this will be accomplished by a competitive renewal of the existing targeted program on this topic.

7. HEART FAILURE AND SHOCK

PROGRAM GOALS

Heart failure and shock may result from many different kinds of heart disease. A better understanding of energy utilization in heart muscle is essential to improve diagnosis, prevention, and treatment of these disorders.

- A major goal is to improve the understanding of energy utilization by heart muscle in heart failure and shock.

The amount of irreversibly damaged muscle is not predetermined at the onset of a heart attack; there is a zone which is in jeopardy but has not yet progressed to irreversible damage. Current research has identified several promising means to protect this zone of potentially reversible damage and to promote its recovery.

- A second goal is to minimize heart failure associated with and following heart attack by enhancing the survival of damaged heart muscle.

Methods to quantify the amount of heart muscle which is inadequately perfused or which has undergone irreversible damage are crucial for the evaluation of therapeutic interventions

- A third goal is to develop more satisfactory means of quantifying the extent of heart muscle which is inadequately perfused with arterial blood or which has undergone irreversible damage.

Other aspects of the diagnosis, etiology, therapy, and prevention of heart failure and shock warrant emphasis. These include research on improving the pumping function of the heart, understanding and treating the disturbances of the regulation of peripheral blood vessels, and the evaluation of altered endocrine and renal function.

- A fourth goal of the program is to improve the understanding and management of heart failure and shock due to cardiovascular causes.

PROGRAM STATUS

Recent Progress. Significant recent progress has occurred in the basic science laboratories and clinical areas. Understanding of calcium-protein interactions in cellular membranes and subcellular organellae of heart muscle has advanced considerably. These interactions, which are affected in heart diseases, can be favorably altered with various newly developed calcium-active agents. This ability to understand and correct depressed contractility of affected heart muscle is one of the most important steps in the eventual control of clinical heart failure and shock.

A major problem in clinical evaluation and control of heart failure and shock has been the accurate determination of that portion of total heart muscle mass which is dead or dying and whether the therapy employed is affecting the diseased rather than normal muscle. In the past year noninvasive methods of testing have advanced markedly. The amounts of heart muscle affected and the changes of diseased muscle under specific therapies can now be determined. Normal, dead, and dying muscle can be visualized by radioisotope techniques. New ultrasonic equipment with multiple, focused signals can scan the inner and outer surfaces of heart and valves with a clarity not envisioned a year ago. The amounts of specific enzymes released from the heart can be used to quantify the total muscle mass being destroyed. These techniques have aided greatly in the development and evaluation of various therapies used to control cardiac muscle damage and to impede the subsequent risk of heart failure and shock. A range of pharmacologic agents as well as mechanical circulatory assist devices have proved beneficial.

Future Challenges. More definitive clinical studies are required to evaluate, on a larger scale, current therapy to enhance the survival of heart muscle. The effects on infarct size must be quantified and survival of the heart muscle assessed. Heart muscle must be studied at cellular and subcellular levels in an effort to develop more effective therapy.

The techniques used to quantify the degree of heart muscle damage must be further validated. Improved techniques would minimize the number of patients needed to evaluate new modes of therapy. Electrocardiographic, enzymatic, and radioisotopic techniques have undergone important developments over the past year and continue to show promise of further important advances.

Studies of heart failure and shock need to be expanded to include other organ systems. The dynamics and the neural and endocrine control of the circulation must be studied in the peripheral circulation as well as in the heart, kidneys, and other organs.

PROGRAM PLANS

Actions. The Institute plans to:

- Enlarge biochemical and physiological studies of the fundamental processes associated with heart muscle survival both in laboratory and clinical studies and, based upon these studies, develop methods for minimizing the extent of heart muscle damage in a heart attack

- Establish clinical studies, contingent upon success of current pilot studies, to assess the therapeutic efficacy of promising techniques for minimizing the extent of heart muscle damage

- Expand the program for quantifying the extent of heart muscle which is inadequately perfused or which has undergone irreversible damage

- Continue the US-USSR cooperative program on myocardial metabolism.

Schedule. Continuing and new actions related to cardiac failure and shock will emphasize the pathophysiology of ischemic myocardium and methods of quantifying this condition, as well as directing attention to the systemic responses to heart failure and shock. A number of promising techniques have progressed to a stage where they are ready for clinical evaluation on a moderate scale; clinical trials may be ready for initiation in FY 75 and FY 76. The program will peak in FY 80 and begin to level off by FY 81.

In the coming year, targeted efforts include a solicitation for the development of methods to protect ischemic myocardium and minimize infarct size, and to quantify the extent of injured heart muscle. There will be competitive solicitations in the current program areas. There may also be a solicitation for a collaborative clinical investigation of techniques for protecting the ischemic myocardium.

8. CONGENITAL AND RHEUMATIC HEART DISEASES

PROGRAM GOALS

Congenital and rheumatic heart diseases are important disorders of childhood and adolescence, and may form the basis for considerable impairment of the quality of life of the patients surviving into adulthood. For the most part, the causes of cardiac defects in the developing fetus are not known.

- The major goals of the program are to understand better the causes of congenital heart disease, to improve diagnosis and therapy, and to rehabilitate patients with congenital heart disease, particularly the newborn.

Rheumatic heart disease is an immunological disturbance that frequently occurs years after initial rheumatic fever and prior streptoccocal infection. Improved understanding of the immunological problems and their control could aid in the identification of susceptible patients and the prevention of rheumatic heart disease. Better control of immunological problems would also improve the success of cardiac transplants and aid in the prevention or treatment of cardiomyopathies and possibly other forms of heart disease.

- Another important goal is to attain a better understanding of the immunological problems associated with heart disease.

Closely related programs which deal with the management of congenital heart diseases in the newborn are discussed in the section on Prevention, Control, and Education.

PROGRAM STATUS

Recent Progress. Recent progress has centered on the improved understanding of fetal cardiac development, better early diagnosis, and corrective surgical therapy. In experimental laboratory animals, highly advanced and miniaturized electronic equipment is being implanted into the in vivo fetus. Hemodynamic changes in the normally developing animal and in animals with induced cardiac defects are being observed during fetal development, normal labor, and early infancy. Correlation of the animal data with changes in normal human cardiac development and in congenital defects has provided insight into better control of the human disease. Also, as a direct result of engineering developments, more accurate early atraumatic diagnosis of human congenital cardiac defects is possible. For example, multicrystal ultrasonic scanning probes placed on the chest wall give accurate pictures of anatomical cardiac defects. These pictures provide the necessary information for appropriate early therapy.

Remarkable advances in surgical therapy, both for congenital and rheumatic defects, are attributable in part to newer engineering developments. Improved design of heart-lung machines, new heart valve designs, and new biomaterials have permitted corrective procedures which were impossible in the recent past. Analysis and evaluation of carefully coded surgical results are important in the final determination of the long-term results and indications for these new procedures.

Advances have occurred in the recognition and understanding of chromosomal abnormalities in the patients with congenital defects which may eventually lead to better understanding of underlying causes of these defects and their prevention.

Future Challenges. A better understanding of both the normal development of the cardiovascular system and the causes of abnormal development is essential for the prevention of congenital heart disease. The roles of maternal infection and toxic exposures during pregnancy are particularly relevant. The emphasis on diagnosis, therapy, and rehabilitation of congenital heart disease patients must increasingly involve the newborn, as well as school-age children. Particular attention must be paid to measures that will assure the first few hours of life. Research challenges in the management of congenital heart diseases in the newborn are closely related to programs discussed in the section on Prevention, Control, and Education.

The role and nature of immune mechanisms as they relate to the heart need to be better understood. Therapy for the suppression of harmful immunological responses must be developed and evaluated.

Both clinical and fundamental research on causes, diagnosis, and therapy of congenital heart disease, rheumatic fever, and rheumatic heart disease must be continued with periodic updating of approaches.

PROGRAM PLANS

Actions. The Institute plans to:

- Establish Specialized Centers of Research in Congenital Heart Disease at two to four locations; emphasize in these centers research topics such as cardiovascular development, improved diagnostic techniques, and improved therapy with particular emphasis on the newborn

- Encourage studies of immunological problems in heart disease and their management, specifically in relation to rheumatic heart disease, cardiac transplantation, and cardiomyopathies

- Continue the US-USSR cooperative study on congenital heart disease.

Schedule. There will be a diminished emphasis on the hemodynamic and surgical aspects of these diseases in older children and adults. Studies of the causes of both congenital and rheumatic heart diseases will be emphasized. For congenital heart disease, there will be an increasing clinical emphasis on the neonatal period.

9. CARDIOMYOPATHIES AND INFECTIONS OF THE HEART

PROGRAM GOALS

Cardiomyopathy and infections of the heart cause enlargement of the heart, heart failure, irregularities of heart rhythms, and occasionally sudden death.

Most cardiomyopathies are of unknown cause (idiopathic cardiomyopathies). Our ability to correct the abnormal process is dependent upon determining the factors which cause this group of heart diseases.

- The goals of the program are to prevent, diagnose, and treat the various cardiomyopathies and infections of the heart, with particular emphasis on improved understanding of their causes.

PROGRAM STATUS

Recent Progress. Recent significant advances in the control of cardiomyopathies and infections of the heart can be attributed in main part to control of the underlying causes and to the improved management of heart failure, shock, and arrhythmias. A better understanding and control of endocrine defects such as thyroid and pituitary malfunction, and the recognition of the toxic effects of agents such as alcohol, have also helped to control some of the most serious defects. Past measures to prevent rheumatic fever and subsequent valvular disease have helped to prevent the development of the most common foci for bacterial endocarditis. Recently developed improved valvular prostheses have decreased the incidence of serious infections which were a major cause of prosthetic valve failures.

Future Challenges. There is a particular need to understand the causes of cardiomyopathies. Since these diseases stem from a variety of causes, research efforts must be broadly based and involve multiple disciplines. Cellular and subcellular biochemical and immunological studies offer opportunities to improve our

understanding of these problems. The role of toxic substances, such as drugs and alcohol, and of viral infections and genetic disorders need to be further investigated. Better diagnostic and therapeutic approaches to these diseases must also be developed.

PROGRAM PLANS

Actions. The Institute plans to:

- Focus attention on studies of the etiologies of cardiomyopathies and infections of the heart, emphasizing epidemiological methods, viral and immunological research, the development and utilization of animal models, and the determinations of mechanisms of myocardial damage by application of biochemical, physiological, physical, and pharmacological techniques. (See section on Congenital and Rheumatic Heart Diseases, under Actions on immunological problems.)

Schedule. As this unresearched field is developed, continuing and new actions with initial emphasis on causation will permit an increase in activity with progressive increases in funding through FY 81.

10. CIRCULATORY ASSISTANCE

PROGRAM GOALS

Present techniques of pharmacological management of acute and chronic cardiac insufficiency and shock still leave a substantial number of patients with compromised or fatally impaired heart function. It is possible to substitute some of the pumping function of the heart and to relieve its workload by mechanical supportive means. At present, such techniques are possible for a brief period in man and for longer periods in the experimental animal.

- A major goal of the program is to develop and assess therapeutically effective, safe, and reliable cardiac assist devices and total heart replacement devices to support or take over the workload of the heart.

Methods to assess and quantify the degree of circulatory impairment are also needed so that patients with all forms of suspected or known heart disease, particularly patients in heart failure and shock, can be evaluated.

- A second goal is to develop the instrumentation and techniques necessary for the assessment of severely impaired cardiovascular performance.

PROGRAM STATUS

Recent Progress. In experimental animals, cardiac assist devices, designed to aid the failing left ventricle, have reversed heart failure. A substantial fraction of animals with such implants became chronic survivors for periods of weeks or months. The application of total cardiac replacement devices is also resulting in more and longer-term survivals. In these experiments, the pumps were actuated pneumatically from outside the body. Engines designed for implantation within the body have been reduced in size. Their efficiency in converting electrical energy or thermal energy, such as that from radioisotopes, into pump actuation has been improved. These engines have now been studied in animals as well as in the laboratory. The pumps have undergone development to reduce their size, increase their reliability, improve their valves, and diminish problems with blood clot formation on the pump lining. Developments have taken place on important related topics, including the control system for the pump, the materials in contact with the blood, the transmission of energy into the body, and the storage of energy within the body. Criteria for the clinical investigative use of left ventricular assist devices have been developed.

Numerous developments have taken place in the field of cardiovascular instrumentation. For example, because of important improvements in the visualization of cardiovascular structures using ultrasonic techniques, it is now possible to provide a better assessment of their function. Implantable blood pressure transducers with greatly reduced zero drift have been developed making them suitable for chronic implantation.

Future Challenges. Mechanical techniques for augmenting or substituting for the pumping of the heart must include implanted permanent ventricular assist devices, totally or partially implanted temporary ventricular assist devices, and emergency temporary circulatory assist devices, as well as total cardiac replacement devices. This requires research on the physiology of assisted circulation as well as refinement of the requisite components of the systems.

The major thrust must be the development of permanent ventricular assist devices; however, this must be approached via the prior development and study of temporary ventricular assist devices.

PROGRAM PLANS

Actions. The Institute plans to:

- Expand research, development, and assessment of temporary circulatory assist devices directed at short-term management of heart failure and shock
- Expand the research, development, and assessment of implantable heart assist devices capable of taking over a significant fraction of the work of the heart for extended periods of time
- Continue research, development, and assessment of implantable heart replacement devices for permanent implantation
- Expand research and development of circulatory assist and artificial heart systems, including the development of biocompatible materials, appropriate pumps, actuators, energy transforming devices, implantable energy systems, transcutaneous transmission of energy, and control systems for these devices
- Expand the systematic physiologic evaluation of ventricular assist and cardiac replacement devices
- Implement the US-USSR Agreement on Cooperation in the field of Artificial Heart Research and Development
- Expand research and development of noninvasive and invasive instruments and techniques for the assessment of cardiovascular performance.

Schedule. Present programs involving the development of circulatory assist devices and total heart replacement devices will continue. The near-term goals emphasize temporary assist devices which will provide substantial clinical benefit rather than the more ambitious goals of a totally implantable and permanently energized long-term cardiac assist or replacement device. Based upon these near-term developments, permanent fully implanted assist devices and, ultimately, cardiac replacement devices will be developed.

There will be selective termination of targeted activities as their objectives are met. Overall program emphasis will focus on the need for large-scale reliability and performance tests prior to clinical utilization of assist devices as well as the advent of long-term devices.

In the coming year targeted efforts will be made to develop, fabricate, and test percutaneous leads for energy transmission; to test physically materials for use in blood pump bladders; to evaluate physiologically ventricular assist and cardiac replacement devices; to develop improved materials for blood pump bladders; and perhaps to develop high-cycle-life and high-energy-density rechargeable batteries for chronic implantation to power artificial heart systems. Left ventricular assist devices currently developed by the Institute's contractors will be validated for clinical investigative use. This will involve both acute and chronic experiments in calves. After successful validation of these devices in animals, short-term clinical investigative studies will be initiated in man.

PREVENTION, CONTROL, AND EDUCATION PROGRAMS

The First Annual Report of the Director emphasized that considerable knowledge is already available on the prevention and control of heart and blood vessel diseases. However, achieving the most effective means for applying this knowledge requires more specific research and evaluation efforts. The Institute's emphasis in its prevention, demonstration, and control programs is to seek immediate application of presently available data for prevention and control and at the same time strive to make prevention and control measures more effective.

Particular emphasis is being placed on the testing and evaluation of a program for the prevention of the two major cardiovascular disorders--hypertension and arteriosclerosis. For these two disorders, a sufficient base of knowledge exists which could effect substantial reductions in morbidity and mortality if this knowledge were implemented through coordinated and comprehensive long-range programs. Prevention or amelioration of other cardiovascular disorders also requires attention. The stages of development of specific programs for hypertension, arteriosclerosis, coronary heart disease, and congenital heart disease are discussed in this section.

To carry out these prevention, control, and education activities, it is necessary to determine the state of the art in continuing education. The Institute intends to assess current developments in the field of continuing education for health care practitioners by conducting a workshop in FY 75. As a result of the discussions of this multidisciplinary group, it is hoped that new directions will be given to research and program activities in this area.

Special attention will be given to maintain liaison and provide assistance to the new National Research and Demonstration Centers as they become established and to help in the development of their demonstration, control, and education programs.

1. HYPERTENSION

PROGRAM GOALS

The effectiveness of antihypertensive drug therapy in reducing the incidence of strokes and heart failure among persons with moderate and severe hypertension is well established. However, less than 20 percent of hypertensives are presently receiving adequate treatment. To bring individuals with moderate and severe hypertension under effective treatment, continued efforts to expand current program initiatives through existing medical networks are urgently needed. Sustained effective blood pressure management in such persons should result in a reduction of disability and death by as much as 40 percent when compared with rates for untreated hypertension.

- A continuing national goal of the program is to motivate all adults to have their blood pressure checked annually and, for those found to be hypertensive, to urge them to obtain proper therapy and maintain therapy on a continuing basis.

- Another continuing national goal is to make current knowledge of antihypertensive drug management more widely available to general practitioners and specialists who treat these patients.

PROGRAM STATUS

Recent Progress. The National High Blood Pressure Education Program (NHBPEP) was initiated in 1972. Recommendations for action by the Program were submitted to the Secretary in July 1973 and implementation of these recommendations was begun in October 1973. To date, the NHBPEP has engendered documented active support of approximately 60 major national organizations and/or industrial groups, some 48 State Health Departments, and numerous local community organizations. A significant degree of coordination has been developed within the Federal government and the private sector as exemplified by the following examples.

- The successful mounting of a National High Blood Pressure Month during May 1974; the development and promulgation of nationally recognized standards for screening, evaluation, therapy, and education of hypertensive patients; and development and operation of an Education Research Program now supporting six investigational efforts.

- The development and operation of a Community Consultation Service which has assisted over 175 communities; the development and operation of a High Blood Pressure Information Center which has responded to over 550,000

requests; and development and operation of an ongoing mass media education campaign which has presented educational messages to an estimated 75 percent of the nation's population.

- The development and operation of an ongoing cooperative professional education effort designed to reach physicians, nurses, dentists, and other health personnel. Development and promulgation of performance characteristics for physicians engaged in detecting high blood pressure are included.

- The development and operation of a program evaluation mechanism which includes baseline studies of public and physician knowledge, attitudes, and behavior regarding high blood pressure; ongoing collection of special information in studies on life insurance, automatic blood pressure measuring devices, and cost benefit parameters.

It is known that about four million individuals have moderate or severe hypertension and that treatment reduces serious complications and deaths. Unfortunately, treatment must be lifelong, individualized, and may be accompanied by side effects in patients who otherwise feel well. Thus, major challenges in the National Program include efforts to help these patients understand their disease, to develop beneficial health attitudes, and to adhere to treatment. An important component of the National Heart and Lung Institute Hypertension Detection and Follow-Up Program (HDFP), described in the section on Research Programs, deals with these problems. In addition to the research aspects of this study, the HDFP also relates to health education and behavioral research requirements as these may affect adherence to therapy and personal attitude towards hypertension.

Future Challenges. Important challenges in prevention and control of high blood pressure continue to include the development of simplified medical regimens using available antihypertensive drugs and the creation of systems which will optimize the utilization of nurses and allied health professionals in educational and therapeutic programs under physicians' supervision. The problem of motivating patients to adhere to long-term antihypertensive drug therapy requires further intensive investigation. Therefore, the Institute intends to conduct further research in this area. In addition, the use of demonstration programs is being explored. These programs will seek effective means to detect, diagnose, and treat hypertension, and to develop follow-up systems in the community in cooperation with existing medical and community health resources.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue the National High Blood Pressure Education Program to expand public and professional knowledge of the dangers of high blood pressure and the benefits of effective treatment through a variety of program components, including a High Blood Pressure Information Center, Community Consultation Service, focused educational programs for health professionals, the general public, and patients

- Continue an education research program to develop new knowledge and methods of education that will increase awareness of the problems, to define cost effective methods of delivering professional, consumer, and patient education; and to identify methods of increasing patient adherence

- Initiate behavioral research related to the Hypertension Detection and Follow-Up Program (see Research Programs in Hypertension) to characterize and evaluate differences in knowledge, attitudes, and behavior between persons with high blood pressure who participate poorly or not at all as compared to those who participate fully in the antihypertensive therapy.

Schedule. This year the National High Blood Pressure Education Program anticipates active expansion of the number of groups using professional and public education materials distributed by the High Blood Pressure Information Center. Community consultation services will be continued and three major national workshops will be held. Education research studies will be conducted as part of the program activities. The health education and behavioral research aspects of the Hypertension Detection and Follow-Up Program will be continued and expanded.

A Program Announcement has been issued to conduct a study to ascertain the characteristics which result in adherence to antihypertensive therapy and to determine the educational interventions that will enhance a patient's initial and long-term adherence to hypertensive therapy. The National Heart and Lung Institute expects to initiate the approved projects in the spring of 1975.

The Institute's activities in hypertension will continue to receive high emphasis and will require sustained support until adequate prevention and control of hypertension is achieved.

2. ARTERIOSCLEROSIS

PROGRAM GOALS

Since arteriosclerotic disease is chronic, slow to develop, and often without obvious ill effects until serious consequences suddenly become manifest, its prevention must be attained in persons who regard themselves as healthy. Moreover, present data suggests that prevention may involve steps to change risk factors and that it will include dietary modifications and changes in habits and lifestyles. It is likely that such changes will not be adopted unless adequate health education of the public results in appropriate health attitudes. This requires an enhanced level of education and communication with better awareness of the psychosocial attributes of arteriosclerotic disease.

Some degree of prevention of atherosclerosis appears attainable. A number of the factors that increase susceptibility to atherosclerosis and coronary heart disease have been well established. These include elevated blood lipids, high blood pressure, and cigarette smoking. These risk factors can be modified, and health professionals and the public need to know how this can be done.

- A continuing program goal is to reduce disability and death from arteriosclerotic disease of the blood vessels of the heart, brain, and extremities through the prevention and control of risk factors.

PROGRAM STATUS

Recent Progress. As a result of the activities of a working group drawn from the National Heart and Lung Institute, the United States Department of Agriculture (USDA), and the Food and Drug Administration (FDA), new food tables containing updated nutrient data for the content of cholesterol, saturated and polyunsaturated fatty acids, complex and simple carbohydrates, minerals, and vitamins are now being developed. The FDA's new voluntary food labeling regulation program and the USDA's nutrient data bank (which has been accepted by the food industry) are now making available additional information on nutrition.

The Institute is also continuing to support certain studies by the USDA's Consumer and Food Economic Institute of the Agriculture Research Service. These include a literature search and documentation and identification of the nutrient composition of foods. The immediate product of this collaborative effort has been the production of a new food nutrient data tape which will be used for both the Lipid Research Clinic studies and the Multiple Risk Factor Intervention Trial.

The nutritional support staffs of both the Multiple Risk Factor Intervention Trial (MRFIT) and Lipid Research Clinic (LRC) trials (see section on Arteriosclerosis under Research) have continued

participation with university groups and with the American Heart Association to explore all available avenues to promote nutrition education. Although the development of education materials and techniques for the MRFIT and LRC trials is the immediate goal, these materials and methods are also appropriate for general use. The Institute's cardiovascular nutritionists are increasingly involved in professional education programs sponsored by voluntary and official agencies. The informational series on the dietary management of hyperlipoproteinemia has been revised and is available for physicians and nutritionists.

Future Challenges. By measuring blood lipids, blood glucose, blood pressure, and weight and by obtaining information on the level of cigarette smoking, it is now possible, and relatively easy, to identify persons who have an increased chance of developing coronary heart disease, stroke, or peripheral vascular disease. Data from an electrocardiogram further improves the predictability of the occurrence of these complications of arteriosclerosis.

Using these risk factors as indicators, it is possible to predict the 20 percent of the population who are most likely to develop 40 percent of the coronary heart attacks, 50 percent of the strokes, and 50 percent of the clinical peripheral vascular events during a subsequent six-year period. Such predictions are not absolute as heart attacks, strokes, and peripheral vascular disease also may occur in persons without such risk factors. However, the highest priority should be given to identification of these high-risk susceptible individuals.

PROGRAM PLANS

Actions. The Institute plans to:

- Encourage experts in psychology, sociology, and behavioral research to investigate problems associated with health education and attitudes, motivation, and compliance as these relate to the prevention of arteriosclerosis, hypertension, or stroke and to the therapy and rehabilitation of patients with these diseases

- Develop and utilize a register of experts from the behavioral and social sciences who can assist the Institute in its program activities

- Continue to cooperate with the Department of Agriculture and other Federal agencies having a nutrition-related interest to establish policies and education programs on the role of nutrition in heart disease; develop, evaluate, and apply dietary survey and counseling methods in the treatment of hyperlipidemia

- Continue to support, in cooperation with the Department of Agriculture and the Food and Drug Administration, a special program to update the information on composition of foods in the American market place.

Schedule. The cooperation with the USDA and FDA is a continuing relationship. The updated nutrient data tape will be available for use before the end of FY 75. The Information Program for risk factor detection and prevention will be increased in FY 76 and receive sustained support thereafter. It is projected that support for nutrition programs will increase substantially in FY 76 and increase incrementally thereafter.

3. CORONARY HEART DISEASE

PROGRAM GOALS

Program goals for the control of coronary heart disease remain the same as those set forth in the previous report. Since about 400,000 deaths annually occur from coronary heart disease prior to hospitalization, emergency medical care for the person with suspected heart attack is a major problem.

- A goal of this control program is to introduce the developments in emergency medical care for the cardiac patient into comprehensive emergency care systems.
- An additional goal is to conduct research on improved methods for rehabilitation.

PROGRAM STATUS

Recent Progress. As yet only modest progress can be reported in this specific area. The Institute continues to support research actions to develop information for the design and evaluation of emergency care systems and is participating with other agencies in an Interagency Committee on Emergency Medical Services.

The Institute recently convened a task force to determine the state of the art of cardiac rehabilitation. The task force report includes recommendations for the provision and expansion of rehabilitation services (education-information and patient services), and demonstration projects.

Future Challenges. A savings in lives and probably a decrease in disability from heart attacks can be expected from improved emergency medical systems for the cardiac patient. Once a heart attack

or other serious cardiac illness has occurred, both the rate and the completeness of return toward normal functioning in society may remain inadequate unless the disability can be minimized and recovery hastened. This requires appropriate attention to the medical and psychological factors associated with cardiac rehabilitation.

In accord with the recommendations by the task force on rehabilitation, the Institute plans to assess the knowledge, attitudes, and behavior of the public and of health care professionals. This data will be used to guide decisions regarding interventions that are needed. These interventions may involve changes in the delivery of health care, development of educational strategies, and/or increased knowledge of and participation in cardiovascular rehabilitation services.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue to contribute, in collaboration with other Federal agencies, to the design and analysis of the cardiac elements of emergency care systems, emphasizing the implementation of research developments under Actions in the Research section on Coronary Heart Disease

- Explore, in collaboration with the Social and Rehabilitation Service, the establishment of demonstration programs for the rehabilitation of patients with cardiovascular disease

- Undertake a baseline survey of the public and of health care professionals to determine their knowledge, attitudes, and behavior in relation to cardiovascular rehabilitation.

Schedule. The schedule for the first action is contingent upon the plans and activities of the principal agencies with responsibility for Emergency Medical Programs; the National Heart and Lung Institute components could be initiated in FY 75 and continued through FY 78. Collaborative efforts on rehabilitation programs were initiated in FY 74 and will be continued through FY 80.

4. CONGENITAL HEART DISEASE

PROGRAM GOALS

Recognition of congenital heart disease is particularly difficult during the newborn period. Yet this is the period during which many deaths from congenital heart disease occur.

- The goals are to develop techniques for the early recognition of cardiac disease in the newborn and to initiate demonstration programs for early recognition and treatment of congenital heart disease.

PROGRAM STATUS

Recent Progress. As previously reported, continuing investigations and the development of a variety of diagnostic techniques, for example ultrasonic imaging, are providing capabilities for more ready and accurate assessment of congenital heart disease. These new methods are being used by nursery staff and physicians for better and earlier recognition of congenital heart disease in the neonate.

Future Challenges. Substantial savings in lives can probably be achieved by early recognition of cardiac problems in the newborn. Specialized groups to deal with these problems are needed throughout the health care delivery system.

PROGRAM PLANS

Actions. The Institute plans to:

- Explore the feasibility of demonstration programs for the early recognition of cardiac (and respiratory) problems in the newborn. Such programs will emphasize intensive professional education, development of instrumentation for improved detection, better interhospital communication and transportation, and the availability of diagnostic and surgical facilities for treating critically ill infants.

Schedule. The program will be initiated in FY 76 and continue through FY 80.

PROGRAM COORDINATION

A number of major cooperative and collaborative efforts in heart and blood vessel diseases with Federal and non-Federal organizations, professional societies, and the private sector are being supported by the National Heart and Lung Institute as fundamental components of the National Program. These efforts include collaboration and cooperation with the efforts of other Bureaus, Institutes, and Divisions of the National Institutes of Health. These include the following examples.

- Smoking. Smoking is one of the risk factors associated with an increased risk of arteriosclerosis and its complications. The Institute collaborates with the National Cancer Institute as well as the Center for Disease Control's National Clearing House for Smoking and Health and the Veterans Administration (VA) on efforts to reduce smoking and its harmful effects on health. The goals of these efforts are to develop a less hazardous cigarette, to study smoking behavior and its modification, and to utilize these findings in developing an intervention program in the general population.

- Nutrition. Nutritionists from the Institute are collaborating directly with the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA) in defining data gaps in order to update and publish a new authoritative nutrient composition source book. This has already resulted in an updated provisional food table for certain important fat-containing food groups, and more will follow in the next few months. Completion of this effort will provide the basic data necessary to enumerate dietary constituents for research on the effects of diet on blood lipids and heart disease.

  An Institute nutritionist is collaborating with the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), the American Diabetes Association, and the American Dietetic Association in an effort to update the traditional diabetic exchange list pamphlet published in 1950. Since diabetes and cardiovascular disease so frequently occur together, the Institute has a natural interest in contributing to the format and content of the new pamphlet.

  An Institute nutritionist is serving on the U.S. Public Health Service Dietetics-Nutrition Career Development Committee which is actively attempting to define needs and opportunities for training and experience for nutrition-related professionals within the Federal health service agencies.

  The Institute staff is participating on an NIH inter-Institute nutrition committee and has also provided consultation to other governmental and voluntary agencies concerning nutrition. These include the Veterans Administration and the U.S. Public Health Service Outpatient Clinics.

- Hypertension. The National Heart and Lung Institute is collaborating with the Veterans Administration in sharing the costs of two clinical research projects in hypertension. The first is a study to determine whether propranolol alone or with hydrochlorothiazide and/or hydralazine reduces arterial blood pressure as effectively as the commonly used combination of hydrochlorothiazide and reserpine. The incidence of side effects from propranolol as well as their gravity will also be assessed.

The second study with the Veterans Administration is a pilot clinical trial of the treatment of mild hypertension. This pilot trial will seek to determine the feasibility of undertaking a double-blind clinical trial to test whether the treatment of mild hypertension results in a reduced incidence of myocardial infarction and death from coronary heart disease. This two-year pilot study in four VA hospitals began screening and enrollment of participants in July 1974. It will determine the feasibility of enrolling a large enough number of participants for a definitive study and provide data on the drop-out rate over a one-year period.

The Institute is also collaborating with the National Cancer Institute on studies to determine the potential carcinogenic effect of the antihypertensive drug reserpine.

- National High Blood Pressure Education Program. The National Heart and Lung Institute has the lead responsibility for coordinating the National High Blood Pressure Education Program (NHBPEP) which is an interagency, Federal/non-Federal cooperative effort. The Health Services Administration, Health Resources Administration, Food and Drug Administration, Veterans Administration, and Department of Defense have all designated representatives to the program. During the first year of the program, the Veterans Administration, Food and Drug Administration, Health Services and Mental Health Administration,* and the National Institutes of Health were represented on four task forces which made recommendations on data base, professional education, community education, and national resources and impact assessment. The Department of Defense was represented on the Professional Education Task Force and assisted in the development of patient education materials.

  Besides representation in the planning effort, several agencies took responsibility for implementing some of the action items during the past year. The Health Services and Mental Health Administration* sponsored the initial development of mass media educational materials; the Food and Drug Administration sponsored a workshop on professional education and is sponsoring a survey of physicians on high blood pressure; the Institute sponsored a public attitude survey on high blood pressure and a national conference on high blood pressure education; the National Heart and Lung Institute is cooperating with the Office of Professional Standards Review, DHEW, to assist Professional Standards Review Organizations (PSRO) to establish model criteria for assessing hypertension care.

  The NHBPEP program has a policy of cooperating with any organization which wishes to produce educational materials, and it

*Since reorganized

will supply technical advice and allow the use of its logo, provided the material does not endorse any particular product(s), is not for sale, and is factually correct. Response from the private sector has been gratifying. Educational materials have been produced with a consistent message for the public and medical professionals. Professional and voluntary organizations such as the American Medical Association, American Heart Association, National Medical Association, American Dental Association, American Public Health Association, and American Red Cross have all endorsed the program. The program also cooperates closely with a newly formed group, the Citizens for the Treatment of High Blood Pressure.

Because hypertension is a significant community health problem, mass screening programs for the detection of hypertension are currently being initiated. Several community groups have asked for guidance in choosing an automated device for measuring blood pressure. Therefore, the Institute, as the lead agency for the National High Blood Pressure Education Program, has initiated a review of the status of automated blood pressure measuring devices with a task force to assess these devices. Representatives from the Food and Drug Administration and the Veterans Administration are among those helping in the evaluation. The Institute will also work with the American Heart Association through the Association's Committee on Criteria and Methods of the Council on Epidemiology. Proposals for evaluating automated blood pressure measuring devices, and for criteria for a suitable device, have been developed by the American Heart Association committees. This work will be of great help to the Institute's Task Force as it attempts to look at all the devices currently available and to assess their suitability.

- Cerebrovascular Disease. A liaison Joint Council Subcommittee has been drawn from the Advisory Councils of the National Institute of Neurological Diseases and Stroke* and the National Heart and Lung Institute, together with other appropriate experts and Institute staffs to coordinate the exchange of information on cerebrovascular diseases. During the past several years, this Subcommittee has served as a focus for information exchange, development of bibliographies, conferences, and workshops on cerebrovascular disease.

- Emergency Medical Services. In the fall of 1972, the Secretary of Health, Education, and Welfare established an Interdepartmental Committee on Emergency Medical Services, with the then Health Services and Mental Health Administration assuming the lead role. This has subsequently been changed to an Interagency Committee, with the Emergency Medical Services Branch

*As of March 14, 1975, name changed to National Institute of Neurological and Communicative Disorders and Stroke.

of the Health Services Administration in the lead role. The Associate Director for Cardiology, Division of Heart and Vascular Diseases, National Heart and Lung Institute, was appointed the National Institutes of Health representative, first to the Interdepartmental and, subsequently, to the Interagency Committee. The Institute has collaborated with the Emergency Medical Services Branch of the Health Services Administration on topics of mutual interest and importance, including cosponsorship of the Second National Conference on Emergency Health Services and of the Meeting on Cardiopulmonary Resuscitation sponsored by the American Red Cross and the National Science Foundation. Within the context of the National Program, the Institute will be responsible for the elucidation of the pathophysiology of heart disease in its earliest emergency phases and for the development of methods of care suitable for incorporation into emergency medical care systems.

- Pacemakers and the Artificial Heart. Collaborative efforts between the Atomic Energy Commission (AEC)* and the National Heart and Lung Institute date back to 1965 when the Commission initiated a program for a radioisotope powered cardiac pacemaker with the consultative advice of the Institute. The reliability of this device, tested in animals by the National Heart and Lung Institute, has been demonstrated at a level sufficient to permit clinical implantation in approximately 50 patients throughout the nation, including several within the clinics of the Institute.

  From the inception of the Artificial Heart Program in the early 1960's, the National Heart and Lung Institute and the Atomic Energy Commission have collaborated to determine the feasibility of an artificial heart and to exchange technological information. Initial feasibility studies were jointly funded and assessed. There has been a renewed and greatly strengthened effort at regular scientific interchange between these two government agencies. Semiannual formal meetings on the development of the artificial heart have been held. Through these contacts and the exchange of documents, the Institute has made available to the Atomic Energy Commission recent progress and research information on its devices and technology program. The Commission, in turn, is making available to the Institute a 33-watt encapsulated plutonium source for conducting important studies on energy sources for artificial hearts.

- Rehabilitation. During the past year, the National Heart and Lung Institute convened a task force to study the present

*Atomic Energy Commission officially became part of the Energy Research and Development Administration (ERDA), January 20, 1975.

state of our knowledge as it relates to cardiac rehabilitation. This task force is assessing the state of the art, the medical and social impact of cardiac rehabilitation, and present techniques and their scientific bases. Recommendations have been developed for implementation of what is known and practical and for initiating effective research where necessary. Representatives from community and governmental agencies (including the American Heart Association, the Council of State Administrators of Vocational Rehabilitation, the Rehabilitation Services Administration, and the Social and Rehabilitation Service) are working closely with the Institute to develop and implement an overall plan on cardiac rehabilitation.

- Cardiac Reconditioning. The National Heart and Lung Institute is collaborating in research on cardiac functions with the National Aeronautics and Space Administration (NASA) to evaluate the effects of weightlessness on cardiovascular function. Previous NASA studies of astronauts returning from space missions indicated that profound, but apparently reversible, changes occurred in various bodily functions. However, the effect of prolonged weightlessness on cardiac function was unknown. Several observations which suggested that the heart may have been affected adversely include: (1) the necropsy studies on the three Soviet cosmonauts who died during reentry suggested that the heart might have undergone severe degenerative changes during their space voyage; (2) the heart size of American astronauts as determined from frontal X-rays was smaller immediately postflight compared to its size preflight; (3) postural hypotension (low blood pressure) was an invariable early postflight finding; and (4) NASA scientists had thought, from the results obtained with techniques then available, that when compared to control preflight studies, cardiac output during exercise shortly after splashdown was often greatly reduced.

  The Institute, collaborating with the biomedical staff of NASA, systematically evaluated the effects of prolonged weightlessness on cardiovascular function of the Skylab III mission astronauts. Preflight and postflight repeat studies of the heart have been completed using the refined technique of echocardiography.

  Because this new technique is noninvasive, many cardiac parameters such as left ventricular end-diastolic volume, end-systolic volume, stroke volume, and cardiac mass could be determined easily 5 days preflight and 1, 2, 4, 11, 31, and 68 days postflight. Also, this technique is more accurate than the older frontal X-ray method of measuring heart size. Previous X-ray measurements indicated erroneously that large decreases in cardiac function occurred with weightlessness. Data obtained from the echocardiographic studies, on the other hand, show that after 84 days of weightlessness, cardiac

function may decrease very slightly but returns to near normal 31 days postflight. Thus, these new studies show that the cardiovascular system adapts well to prolonged weightlessness and suggests that alterations in cardiac dimensions and function are unlikely to limit man's future in space. The methods used in these studies could be applied to measure accurately and noninvasively cardiac function in certain cardiac abnormalities and provide previously unavailable insight as to the reversibility of such abnormalities.

- Congenital Heart Disease. The National Heart and Lung Institute and the National Institute of Child Health and Human Development will coordinate efforts to determine the role of various factors in the development of congenital heart disease. These factors include infections, drugs, and other toxic exposures during pregnancy.

- Manpower Development. The National Heart and Lung Institute has collaborated with a number of professional and private organizations to conduct an indepth assessment of current status of and future needs for manpower in a variety of disciplines related to the National Program in heart and blood vessel diseases. Examples of cooperating organizations are the American College of Cardiology, American Association for Thoracic Surgery, and the American Heart Association.

- International Collaboration. Since the cardiovascular disease problems addressed by the National Program are major problems encountered by all peoples throughout the world, the National Heart and Lung Institute participates in a number of international efforts. Implementation of the National Program provides an opportunity for exchange of information between countries on problems related to all areas of the National Program. The planned research and prevention, control, and education programs in the United States can be greatly enhanced through cooperation with other countries which are trying to solve similar problems within their own borders.

  The Institute coordinates the US-USSR Health Exchange Program in the cardiovascular area. This is a highly structured, collaborative international program related to the goals of the National Program.

Key activities related to the National Program which are being implemented under the US-USSR agreement are briefly described below:

- Pathogenesis of Arteriosclerosis. Arteriosclerosis is the most common type of cardiovascular disease and the chief cause of death in both the U.S. and the U.S.S.R. A joint

clinical study has been undertaken to determine the prevalence in both countries of hyperlipidemias and ischemic heart disease, and the effect of diet on the risk of developing these diseases. This is the first study of its kind in the world. It involves large numbers of well-characterized subjects in two countries, comprehensively studied according to identical techniques based on carefully worked out research protocols, and analyzed by highly standardized methods.

- Management of Ischemic Heart Disease. Ischemic heart disease is the most common clinical complication of arteriosclerosis and the most common complication leading to death. The U.S., through the NHLI, and the U.S.S.R. are conducting a comparative study of different approaches for medical and surgical treatment of ischemic heart disease. This project, also the first of its kind, will evaluate and compare the chronic angina and heart attack disability treatment methods that have been developed in each country.

- Myocardial Metabolism. This topic involves the study of activities and functions of both the healthy and the diseased heart. Thus, it is relevant to the study of all types of heart disease. During the past year, American and Soviet scientists have exchanged information on methods to limit the extent of heart muscle damage by heart attack. These findings will be published jointly.

- Congenital Heart Disease. Congenital heart disease affects an estimated 25,000 children born in the U.S. each year and a corresponding number born in the U.S.S.R. each year. The objectives of this collaborative study are to develop diagnostic techniques and methods of postoperative care, to study the mechanisms of development of pulmonary hypertension, to search for new ways of reducing mortality from the surgical treatment of Tetralogy of Fallot (a congenital malfunction of the heart involving four distinct defects), and to study diagnostic techniques and surgical treatment of complex heart defects.

- Sudden Death. This problem is a new initiative for collaboration in the cardiovascular area. Exchange of information, exchange of health professionals, and meetings between Soviet and American specialists are in progress to develop detailed plans for scientific cooperation.

In light of recent progress and future challenges the actions and schedules for these programs are updated annually by the Joint US-USSR Committee which meets every year either in the United States or the Soviet Union.

A second US-USSR agreement in the cardiovascular area was initiated in June 1974 in Artificial Heart Research and Development. This program is also administered by the Institute.

MANPOWER RESOURCES

The area of Heart and Blood Vessel Diseases has historically been responsible for the largest segment of the National Heart and Lung Institute's training programs with approximately 1400 individuals (1200 postdoctoral, 200 predoctoral) in full time training status in 1972-73. In 1973, estimates of research manpower needed just to maintain current manpower levels were made by both Institute staff and the professional leadership of the American Heart Association. The two estimates were similar and ranged between 400 and 500 new investigators per year. It was also noted that there is virtually no overlap with the training programs of other units of the National Institutes of Health or, more broadly, of the Public Health Service.

Using an average duration of two and one-half years for postdoctoral training the above program might seem adequate to meet this need. However, evidence of a shortfall of previous training efforts was revealed in a 1971 survey by Hammersten and Comroe which showed more than 200 funded unfilled cardiovascular faculty vacancies in medicine, pediatrics, and surgery departments of medical schools in 1971. A total need for more than 1200 new instructors by 1976 was projected. Other independent surveys have provided similar figures.

In addition to the general needs already cited, several specific needs were identified by the Institute and its advisors in 1972 and these needs have since expanded with the Institute's increased activities mandated by the National Heart, Blood Vessel, Lung, and Blood Act. These needs include behavioral scientists; basic investigators; biomedical engineering specialists; population geneticists; protein and immunochemists; investigators with specialized training in endocrinology and metabolism; experts in studies on coagulation; individuals with expertise in fundamental nutrition, lipid metabolism, growth, and development in pediatrics; epidemiologists; and biostatisticians.

Needs were also identified by the Institute for physicians with special training to fill vacancies in hypertension control programs and for nutritionists to participate in Multiple Risk Factor Intervention Studies, Lipid Research Centers, Specialized Centers of Research, Hypertension Detection and Follow-Up Programs, Health Information, Prevention and Control Programs, and National Research and Demonstration Centers.

In addition to the above needs, the high incidence of hypertension in the black urban population poses a specific problem in relation to our mandate in this area. The paucity of black investigators and instructors not only impairs communication with the population at risk but is also so severe that it makes the usual training recruitment ineffective. Individuals are needed to conduct basic and clinical research, to work with primary care physicians, and to make the black urban population aware of the dangers of untreated hypertension.

LUNG DISEASES

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 states that ". . . chronic lung diseases have been gaining steadily in recent years as important causes of disability and death . . . chronic respiratory diseases affect an estimated ten million Americans, emphysema an estimated one million, chronic bronchitis an estimated four million, and asthma an estimated five million . . . ."

Diseases of the lung constitute a major national health problem of increasing dimensions. In the United States, lung diseases covered by the Program account for an estimated 150,000 deaths each year, cause 45 million days lost from work, 40 million days of bed-restricted activity, and cost the economy approximately $6 billion a year in lost productivity and wages and medical care costs.

In September 1972, the National Heart and Lung Institute appointed the Lung Diseases Panel to develop and recommend a program responsive to the legislative requirements of the National Heart, Blood Vessel, Lung, and Blood Act of 1972.

The recommendations of the Lung Diseases Panel were reviewed by the Institute, the National Heart and Lung Advisory Council, and the Interagency Technical Committee, and formed the basis for developing the Institute's expanded program on lung diseases, as well as for developing the plans for coordination of the overall National Program in lung diseases. The lung program, as initially formulated by the Lung Diseases Panel, has been reviewed and updated annually by the Institute. The updated National Lung Diseases Program presented here reflects the thinking of the Institute staff, the Pulmonary Diseases Advisory Committee, and the lung community of physicians and biomedical scientists to which the Institute looks for professional judgment and advice. It represents an orderly expansion of the Institute's activities relative to pulmonary diseases.

The First Annual Report of the Director of the National Heart and Lung Institute, February 13, 1974, identified some achievements of the lung community toward implementing recommendations of the Lung Diseases Panel. The program continues to be responsive to the legislation which encourages special attention to childhood diseases, chronic lung diseases, and the establishment of National Research and Demonstration Centers. The Institute's program, which addresses immediate as well as long-range objectives, centers on three specific approaches of comparable importance and urgency:

- Research on the structure and function of the lung in order to gain fundamental information which will improve our understanding of important factors in the promotion of health and the prevention and treatment of lung diseases

- Expansion and development of our knowledge base of specific diseases which constitute national health problems, but which represent areas where current information is insufficient to provide immediate solutions

- Application of available technical resources to solve specific problems, solutions of which are expected to pay immediate dividends in improving the health of our nation.

The updated program goals, program evaluation, and program plans are discussed below for each of the eight program areas:

1. Structure and Function of the Lung
2. Pediatric Pulmonary Diseases
3. Emphysema and Chronic Bronchitis
4. Fibrotic and Immunologic Lung Diseases
5. Respiratory Failure
6. Pulmonary Vascular Diseases
7. Inhalation Diseases
8. Respiratory Assistance.

The disease categories addressed by the National Heart and Lung Institute do not include cancer of the lung, which is the purview of the National Cancer Institute, or acute upper respiratory infections or tuberculosis, which are the responsibility of the National Institute of Allergy and Infectious Diseases.

Before discussing the scientific aspects of the National Program in lung diseases, a summary description is presented (in italics) of the lung and the major problem areas within the National Program.

DEFINITIONS OF MAJOR PROBLEM AREAS

This section provides a framework in nontechnical language to help the nonspecialist understand the subsequent discussions of specific pulmonary programs. It summarizes:

1. *The lung: Its components and functions*
2. *Major problem areas.*

1. THE LUNG: ITS COMPONENTS AND FUNCTIONS

The principal (respiratory) function of the lung (Figure 6) is as a gas exchanger; that is, to provide oxygen to the blood and to remove excess carbon dioxide from the blood.

The nonrespiratory (non-gas-exchange) functions of the lung include those processes which are performed by components of the lung to maintain the lung's capability as a gas exchanger.

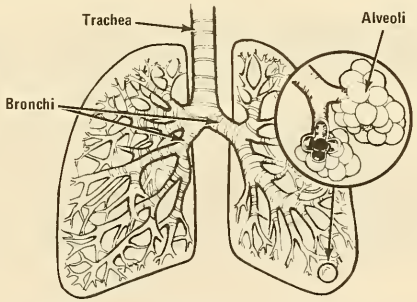


Figure 6. Schematic Diagram of the Human Lungs

The Respiratory Process

The major function of respiration is to provide oxygen to the cells of the body and to remove the excess carbon dioxide from them. In man, respiration has two components: (1) a blood circulatory system to carry oxygen from the lung capillaries (see italics section under Heart and Blood Vessel Diseases) to the tissue cells and carbon dioxide from the tissue cells to the lung capillaries, and (2) a respiratory system or gas exchanger to load the blood in the lung capillaries with oxygen and to remove excess carbon dioxide from it. Figure 7 gives a schematic representation of the gas exchange in the lung. Because of the unique physicochemical properties of hemoglobin (see italics section under Blood Diseases and Blood Resources), high concentrations of oxygen and carbon dioxide can be transported by the blood.

The respiratory system proper includes the following structures: the nose, pharynx, larynx, trachea, bronchi, and lungs. The respiratory system provides a specialized mechanism for presenting large volumes of gas to large volumes of blood in a relatively small space. It is an air pump which draws fresh air through air tubes to millions of small air sacs (alveoli) in the lung. These air sacs have very thin membranes. The respiratory system is a very complex distributing system. It begins as two nasal tubes which are joined in a tube called the trachea (see Figure 6). The trachea divides into two main branches called the right and the left bronchi, and each of these, in turn, divides into two more and each again divides until there are twenty-three subdivisions in all. Twenty-three subdivisions of this type produce several million terminal tubes called bronchioles. A respiratory bronchiole enters an alveolar duct (see Figure 6) which in turn leads into an alveolar sac resembling a bunch of hollow grapes. It is in the alveoli that gas exchange occurs. There are approximately three hundred million alveoli in the human lungs. The surface area of the alveoli, that is the membrane available for the transfer of gases, is large--about 70 square meters, or approximately 40 times the surface area of the body.

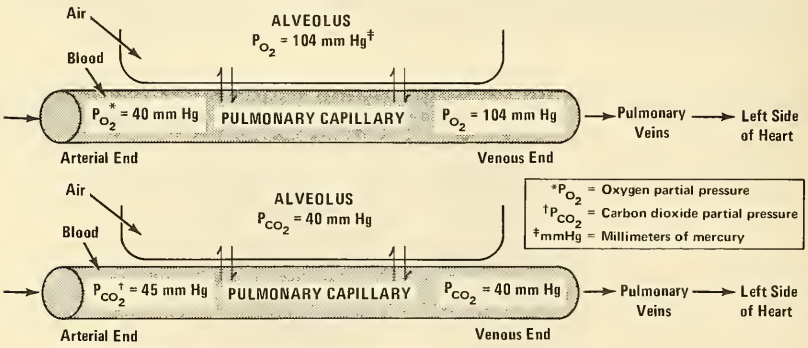


Figure 7. Schematic Representation of Gas Exchange on the Alveoler Capillaries of the Lung

The airways leading to the alveolar ducts (nasal tubes, trachea, bronchi, and bronchioli) are lined with tissue that secretes mucus and moves the mucus in an "upward" direction through the motion of microscopic cilia, or hairlike structures. In this way, foreign particles trapped on the sticky (mucosal) surface are removed to the outside.

Nonrespiratory Components and Functions

The lung consists of more than 40 different types of cells, making it one of the most heterogeneous organs in the body. Among these cells, one of the most important is the Type II epithelial cell which is involved in repair of damaged epithelial cells and in surfactant (pulmonary surface active material) production. The surfactant is secreted onto the alveolar surface where it assists in maintaining the size and shape of the alveolae in a configuration which permits optimal gas exchange to occur.

Lung connective tissue contains collagen (the main supportive protein of all connective tissue) and elastin (the essential fibrous protein of the lung). Multiple types of collagen occur in the lung. Normally, there is a balance between the synthesis and breakdown of collagen and elastin in the lung. In healthy individuals, the enzymes (biological catalysts) which break down these two lung proteins are held in check by inhibitors.

Metabolic functions of the lung are important in diseases of the lung and, possibly, may also affect distant organs. These metabolic functions include the lung's ability to release pharmacologically active substances (e.g., histamines) in hypersensitivity responses (anaphylaxis) to inhalation of, for example, allergens such as pollen. These functions have special relevance to the control of blood pressure, allergic diseases such as asthma, and lung diseases induced by drugs and environmental pollutants.

2. MAJOR PROBLEM AREAS

Respiratory diseases that represent national health problems include chronic obstructive pulmonary diseases (COPD), acute respiratory distress syndromes (RDS), and fibrotic and immunologic lung diseases. The economic cost of these diseases has been estimated at $6.3 billion per year.

Lung diseases afflict both the young and the old. In the newborn, the most common cause of death is the neonatal respiratory distress syndrome. Neonatal RDS is implicated in the development of adult respiratory diseases as well. Fibrotic and immunologic lung diseases are a major cause of lung problems in the young adult, and may cause COPD. Of the adult respiratory diseases, emphysema and chronic bronchitis are the major causes of death. An estimated 10 million Americans are currently affected by these diseases. Together with asthma, emphysema and chronic bronchitis represent a particularly pressing health problem since the death rate and prevalence of these conditions have been increasing at an alarming rate over the past 15 years. As a disabling disease, emphysema is the third

leading cause of worker retirement on social security disability payments. Seven major problem areas in the National Program are defined below:

Pediatric Pulmonary Diseases

Pediatric pulmonary diseases present health problems of national dimensions. Hyaline membrane disease (neonatal respiratory distress syndrome), cystic fibrosis (an inherited disease of abnormal mucus secretion), and bronchiolitis (acute airway obstruction in young children) are among the most important disorders of childhood that involve the lung and the airways. About 40,000 babies are born each year with hyaline membrane disease. Many of these will die unless given prompt treatment, presently unavailable except in a few specialized facilities.

Cystic fibrosis occurs in about one of every 2,000 live births and approximately 5 percent of the general population in the United States carries the gene for this disorder. Cystic fibrosis is one of the main causes of chronic illness in children and young adults and accounts for most of the deaths from pulmonary disease in the pediatric age group. Bronchiolitis is a common pediatric disorder, but data are not available on its incidence.

Emphysema and Chronic Bronchitis

Emphysema and chronic bronchitis are among the major causes of mortality and illness from pulmonary diseases. Emphysema is a disease in which the thin walls in the alveoli (air sacs) lose their elasticity and tear. Chronic bronchitis refers to a persistent inflammation of the lungs characterized by recurrent coughing and excess mucus in the airways. These diseases may be associated with certain risk factors, such as cigarette smoking, and in some cases with genetic determinants (e.g., deficiency of $alpha_1$-antitrypsin enzyme). Emphysema is a leading cause of death in this country and an even greater cause of disability. Data from 1967 indicate that chronic bronchitis and emphysema account for half of the total 181,000 man-years lost due to lung diseases. The crude death rate for chronic bronchitis doubled between 1950 and 1967. The death rate for emphysema increased thirteen-fold in the same period to a level of 10.6 per 100,000 population. Since 1968, the rate decreased 10 percent for chronic bronchitis and 12 percent for emphysema.

Fibrotic and Immunologic Lung Diseases

Fibrotic and immunologic lung diseases are induced by many factors. Fibrotic responses (proliferation of connective tissue or scar formation) and immunologic responses are characteristic of a variety of lung diseases. Among the factors that may induce these responses are exposure to substances such as coal dust, silica, and asbestos in the environment; viral and bacterial infections; diseases of the connective tissue such as rheumatoid arthritis, lupus, and scleroderma; radiation damage; and exposure to substances like molds and dust that initiate hypersensitivity reactions. Diseases characterized by pulmonary fibrosis and/or immunologic reactions include pneumoconiosis, sarcoidosis, diffuse hypersensitivity pneumonitis, farmer's lung, and bronchial asthma. This group of lung diseases is

a major national health problem, second in magnitude among lung diseases only to emphysema and chronic bronchitis.

Statistical data on fibrotic lung diseases are inadequate because these diseases are difficult to diagnose and poorly reported. However, their national health impact is far greater than is generally appreciated. For example, sarcoidosis is about 12 to 15 times more common among blacks than among whites in this country, and now outranks tuberculosis as a cause of disability from pulmonary insufficiency in black populations. It is also more common in women.

Among immunologic lung diseases, asthma is the most common, affecting about 6 million persons in this country (approximately 3 percent of the population). It is responsible for 5 percent of all chronic disabilities and causes an annual loss of about 4 million workdays. Other immunologic lung diseases are associated with specific occupations where exposure to organic dusts or molds is high; for example, farmer's lung in the north central states, bagassosis among sugar cane workers in the south, and hypersensitivity pneumonitis from organisms growing in humidifiers and air conditioners. While none of these diseases is very common in the general population, their importance stems from their high incidence in particular environments.

Respiratory Failure

Respiratory failure is a complication of many nonpulmonary diseases. Acute respiratory distress syndromes have been recognized as such only recently. For these two reasons, data on incidence are not available. A conservative estimate is that 150,000 adult cases of acute respiratory distress syndrome occur each year in the United States with a mortality rate of 40 percent. These figures do not include failure due to chronic pulmonary disease (see italics section on Emphysema and Chronic Bronchitis), nor do they adequately reflect the true incidence because so many cases are unreported.

Pulmonary Vascular Diseases

Pulmonary vascular diseases include cor pulmonale, pulmonary hypertension, and pulmonary edema. Cor pulmonale refers to enlargement of the heart due to an increased workload of the right ventricle resulting from conditions which affect the pulmonary circulation. Pulmonary hypertension is characterized by elevation of pulmonary arterial pressure above normal levels. The condition is considered primary when found in the absence of cardiac or pulmonary diseases and secondary when associated with these diseases. Primary hypertension may be caused by factors such as high altitude and low oxygen, or ingestion of certain drugs and chemicals; secondary hypertension may result from destruction of the pulmonary vascular bed, congenital heart disease, pulmonary vasoconstriction, or congestive heart failure. Pulmonary edema, difficult to detect early, is a pathologic state in which there is abnormal extravascular storage of fluid in the lung. Reliable data on the incidence and prevalence of these diseases are not available. However, it has been estimated that cor pulmonale alone occurs in 40 percent of cases of emphysema and chronic bronchitis, both of which are chronic respiratory diseases of national impact.

Inhalation Diseases

Inhalation diseases are becoming more prevalent in the United States as industrialization and the technological age progress. Of all occupational illnesses, dust inhalation diseases, or pneumoconioses, are the most serious health problem. The dusts inhaled are so fine that they escape the natural cleansing mechanism of the upper respiratory tract and lodge permanently in the lungs. If exposure is sufficiently high and prolonged, the accumulated particles may cause fibrosis or scarring of the lung tissue and in many cases lead to serious disability and even death. One of the most serious problems in our country today comes from the direct handling of asbestos by some 200,000 workers and by another 3 to 5 million persons who are secondarily exposed to the dust. Asbestos is believed to be a leading factor in the deaths of over 2,000 persons each year in the U.S. The breathing of quartz dust, or silica, is another hazard which gradually causes irreversible damage to the lungs. Of the more than 125,000 workers now engaged in coal mining in the United States, an estimated 10 to 20 percent have coal worker's pneumoconiosis, or "black lung." Beryllium, iron, tin, and barium dusts are also hazardous to the lung tissue. Pneumoconioses are also caused by organic dusts from plants such as cotton (byssinosis), sugar cane (bagassosis), and moldy hay (farmer's lung).

Respiratory Assistance

Respiratory assistance can be provided by mechanical devices (ventilators or membrane oxygenators) that support the gas transfer functions of the lung when, as a consequence of the disease, the lungs are unable to maintain proper levels of oxygen and carbon dioxide. Ventilators are devices that mechanically inflate the lungs and can deliver increased amounts of oxygen. Membrane oxygenators are externally placed "artificial lungs" which are connected with the patient's circulatory system. Blood from the patient enters the oxygenator, carbon dioxide is removed, the blood is oxygenated, and then returned to the patient's circulatory system. At present, oxygenators can only be used safely for several days. Recent experience suggests that this method of respiratory assistance holds promise for treatment of some patients in acute respiratory failure.

RESEARCH PROGRAMS

1. STRUCTURE AND FUNCTION OF THE LUNG

PROGRAM GOALS

Our capability to deal with problems of pulmonary disease is severely limited by lack of fundamental knowledge about the structure of the lung. Such knowledge is essential to the development of definitive preventive and therapeutic measures. Current remedies are not only very costly but are also only temporary solutions which need to be replaced by more specific and longer-term methods yet to be discovered through research. Thus, an important priority in the Institute's lung diseases program is to expand research in basic scientific disciplines, such as molecular biology, biochemistry, immunology, and

ultrastructural anatomy. Results of such research can lead to advances in combating all forms of pulmonary disease.

- While it is essential to first focus on studies of the cellular biology of the normal lung, the ultimate goals of this program are to increase understanding of the disease processes and to develop effective methods for prevention, diagnosis, and therapy of lung diseases.

PROGRAM STATUS

Recent Progress. Over the past year progress has been made in fundamental studies to elucidate lung disease mechanisms. The lung, which is made up of approximately 40 specific types of cells, is an organ of numerous functions that include gas exchange, defense against diseases, and removal of inhaled substances. The biochemical and structural characteristics of isolated cell systems have been studied in conjunction with investigation of lung cells in vivo. Viable alveolar Type II epithelial cells have now been isolated from animal lungs. Although the yield of cells is low, they are metabolically active and thus can be used for biochemical studies. Evidence indicates that Type II cells are the site of synthesis of pulmonary surfactant and that they are key cells in the repair of damaged alveolar epithelium. The availability in tissue culture of pure populations of lung cells opens the possibility of correlating biochemical and structural alterations in specific types of cells.

Four new multidisciplinary programs that emphasize correlation of lung strucutre and function were initiated this past year. One project focuses not only on defining the chemical and physical properties of the alveolar cellular and acellular components (e.g., elastin or collagen) but also on morphologic characteristics. Another project represents the combined efforts of investigators with expertise in the areas of immunology, electron microscopy, and tissue culture to study host defense reactions of the lung. A third project is concerned with the chemical composition of connective tissues of the normal lung. The fourth is attempting to define chemical, physiological, and morphological interrelationships among the connective tissue components of lung tissue.

Collagen is the most abundant protein in the lung. Techniques have been developed to study lung collagen synthesis using lung slices, lung tissue culture, and lung cell-free components. It has been demonstrated that at least three genetically distinct types of collagen chains can be synthesized by animal lung tissue slices in vitro. These collagen chains have been shown to be biochemically similar to collagen isolated from other parts of the body (for example in skin and cartilage).

A targeted research program was initiated to study lung elastin, with emphasis on separation and characterization of the components of the elastin fiber, the nature of the precursor of elastin, and changes of elastin with age and species. Although elastin is a principal

component of lung connective tissue and confers the essential property of elasticity, the site of synthesis of elastin and the nature of its structure in normal and pathological states has yet to be determined. Elastin from animal lung tissue has been shown to have a 10 to 20 times higher concentration of a dipeptide combination of the amino acids valine and proline than any of the other structural proteins, including collagen and acidic glycoprotein. These studies can be built upon to develop a specific quantitative assay for elastin that will allow it to be traced through the entire history of synthesis, cross-linking, fiber formation, enzymatic digestion, and turnover in the lung.

Future Challenges. The next several years of research activity should provide information relating structural and biochemical characteristics of individual lung cells. As this information becomes available, investigations into the molecular basis of lung disease should be possible.

Specific opportunities and needs for the future continue, as in the past, to include studies of the quantities and composition of various components in normal lung tissues, their chemical percursors, mechanisms of development, and possible variations with age, sex, and environmental influences. Structural proteins, lipids, and hormones may be involved in diffuse pulmonary fibrosis and in various types of obstructive disease of the airways. The in vivo balance and interaction among proteolytic enzymes and their potential for altering the connective tissue in the lungs need to be elucidated. The turnover rates of lung cells and alterations in these rates with disease require further study.

The structure, synthesis, and physicochemical properties of bronchial mucus, one of the defense mechanisms of the lung, need to be investigated. Although work has been initiated on the control of mucus secretion and mucus composition, one of the problems in dealing with studies of normal pulmonary mucus is the small quantities of pure mucus which are available. Progress has been made in elucidating the physical and chemical properties of mucus and in evaluating the effects of various environmental influences on mucociliary transport. Since evidence suggests that there is some basic structural property of mucus that is essential for effective mucociliary transport, multidisciplinary studies involving physical chemists, biochemists, and pulmonary specialists will be required to define the conditions responsible for the proper functioning of the epithelial mucosa.

Pulmonary physiology must be correlated with new knowledge of molecular biology, structure, and function. Physiologic studies will be continued so as to provide information on the mechanical properties of the lungs and the pulmonary blood vessels, and the coupling of mechanical events to the neurological control of ventilation.

PROGRAM PLANS

Actions. The Institute plans to:

- Expand studies on nonrespiratory functions of the lung by (a) encouraging investigator-initiated research, (b) continuing targeted studies of lung cell separation and culture, and (c) extending targeted programs to include metabolic studies of individual cells

- Extend interdisciplinary studies correlating lung structure and function, particularly with regard to normal lung development and alterations in lung injury by (a) encouraging investigator-initiated grants and program projects, and (b) expanding Specialized Centers of Research to foster collaboration between basic scientists (especially biochemists, immunologists, and cell biologists) and pulmonary clinicians.

Schedule. A new program in lung cell identification will be initiated and a workshop will be held on lung cell separation and culture. Synthetic inhibitors of the enzyme elastase have been prepared and will be distributed to the research community. A workshop will be sponsored to encourage research on metabolic functions of the lung. A program on composition of respiratory mucus will be developed. Continuing and new actions in pulmonary structure and function will be divided between multidisciplinary and specific approaches with gradually increasing activity through FY 79.

2. PEDIATRIC PULMONARY DISEASES

PROGRAM GOALS

Among childhood disorders involving the lung, cystic fibrosis and hyaline membrane disease (neonatal respiratory distress syndrome) are health problems of national significance. Except where treated by the most sophisticated techniques, about half of those born with hyaline membrane disease will die. Bronchiolitis, one of the major obstructive airway diseases of children, may be important in the development of adult chronic lung disease.

The causes of hyaline membrane disease, the nature of cystic fibrosis, and the long-term effects of bronchiolitis require further study.

- Until research has uncovered ways to prevent hyaline membrane disease, early diagnosis and prompt initiation of therapy are essential to save the lives of babies born with this disorder. Primary goals of this program are to develop improved methods for early diagnosis and to design more effective modes of therapy.

- Present modes of therapy for cystic fibrosis are, at best, palliative. A continuing goal is to develop a rational basis for therapy through an understanding of the pathogenesis of this disease.

PROGRAM STATUS

Recent Progress. Because untreated neonatal respiratory distress syndrome has such a rapid downhill course, research on accurate early diagnosis has elicited a high level of interest. Investigators are capitalizing on the findings of fundamental research, particularly those pertaining to the formation and physical and chemical characterization of the surface-active material of the lung (surfactant). Especially significant are tests that predict the degree of lung maturation from analysis of amniotic fluid.

Recent studies have confirmed earlier observations that the lecithin-to-sphingomyelin (L/S) ratio is abnormal in cases of lung immaturity. Earlier arguments against using this ratio to predict abnormality in lung development were based on evidence that the method of determining lecithin may not have identified all the pulmonary surface-active lecithin which has been synthesized. However, with various technical modifications, the most recent studies have examined all lecithins in the amniotic fluid and substantiated the initial findings relative to respiratory distress syndrome. Moreover, the validity of this test appears now to have been corroborated by another test, the foam test, which measures the phospholipid content of amniotic fluid.

Recent work has definitely established the presence of specific proteins in the surface-active material. Moreover, these proteins have been isolated in soluble form and can be utilized for quantitative immunologic assay of surface-active material in human amniotic fluid. Figures for the level of surfactant apoprotein (the protein portion of the surfactant molecule) correlate well with L/S ratio data. Moreover, this assay appears to be a good predictor of the risk of respiratory distress syndrome in the newborn.

Elastin is a component of the normal lung which plays a role in its mechanical function. Studies have shown that the amino acid composition of elastin of the mature lung is different from that of the developing lung, and that the mature pattern is not achieved until the 32nd to 35th week of fetal life. The amino acid composition of the lung elastin in infants dying of hyaline membrane disease is comparable to that of a fetus 20 to 30 weeks of age.

It was feared that infants with hyaline membrane disease may show an increase in mental retardation because of brain damage due to anoxia. Initial data from follow-up studies of such infants show no increased mental retardation as a consequence of hyaline membrane disease.

Cystic fibrosis (CF) is the most frequent lethal hereditary disease of whites in the United States. Although cystic fibrosis affects

many organs, the pulmonary impairment, which may be related to recurrent infections and abnormalities, including an increase in mucus production, commonly causes disability or death. The Institute's program seeks to evaluate cardiac and pulmonary functions and their alteration with therapy. The biochemistry of the mucus abnormality is also being investigated.

Tests used to identify cystic fibrosis are being evaluated. Among the problems under consideration are the reliability of data on "cystic fibrosis factors" in serum and tissue-culture fibroblasts, and their relation to diagnosis of CF in the homozygote (both genes are CF) and heterozygote (one gene is CF) in fetal life, infancy, and childhood.

Several groups are engaged in research on methods for early diagnosis of airway disease in newborn and young children. A spirometer designed for compliance measurements in premature and term newborn infants is now beyond the development stage. A system which is designed to measure pressure-volume curves of the lung and thorax, and functional residual capacity in anesthetized subjects, is also being evaluated. Investigators have initiated a long-term study of effects of lower respiratory tract viral illness in children on subsequent development of lung disease in the adult.

Future Challenges. In order to develop methods of modifying or preventing the disease, a better understanding is needed of the biochemistry and molecular biology of surfactant during normal maturation and during hyaline membrane disease. This continues to be a major challenge. Therapy for hyaline membrane disease should be improved by development of new devices and better approaches to initiate treatment as early as possible. The efficacy of present methods of treatment needs to be assessed and knowledge about such methods widely disseminated. Improved understanding of the etiology and pathogenesis of hyaline membrane disease, as well as new methods of prevention and improved therapy, are anticipated.

An educational program on hyaline membrane disease is being developed for persons outside major medical centers who are involved in prenatal and neonatal care such as physicians, nurses, and midwives. (See section on Prevention, Control, and Education Programs.)

As more infants are now surviving after hyaline membrane disease, it is important to evaluate them for subsequent alterations in pulmonary, neurological, and physiological functions.

An important issue in the study of cystic fibrosis is the production of a factor that inhibits ciliary action.

PROGRAM PLANS

Actions. The Institute plans to:

- Expand basic studies of changes associated with hyaline membrane disease and cystic fibrosis by (a) encouraging investigator-initiated research on biochemical and physiologic features of the prenatal and neonatal environment that predispose to hyaline membrane disease and on the biomedical and biophysical alterations of mucus in cystic fibrosis, and (b) extending interdisciplinary studies of hyaline membrane disease and cystic fibrosis in Specialized Centers of Research

- Initiate targeted programs to (a) develop techniques and devices to assess pulmonary function in infants and young children, and (b) utilize these techniques and devices in longitudinal studies to assess the long-term aftereffects of hyaline membrane disease and bronchiolitis and determine the natural history of cystic fibrosis

- Initiate controlled clinical trials to evaluate the efficacy of widely used--but inadequately assessed--approaches and devices for the therapeutic management of cystic fibrosis and childhood asthma, especially physiotherapy, bronchodilators, and other pharmacologic agents.

Schedule. Because recent findings hold great promise for an effective therapeutic approach to hyaline membrane disease, and because of increasing awareness of the contribution of the pulmonary manifestations of cystic fibrosis to morbidity and mortality from this childhood disease, the programs in pediatric pulmonary diseases will continue to increase through FY 77. Then moderate increments are anticipated through FY 79.

3. EMPHYSEMA AND CHRONIC BRONCHITIS

PROGRAM GOALS

Chronic obstructive pulmonary disease (COPD) is a major problem in this country. Emphysema and chronic bronchitis are the two main diseases which, when considered together, are referred to as COPD. Both emphysema and chronic bronchitis produce breathlessness, cough, and increased susceptibility to respiratory failure and death. COPD attacks middle-aged men and women and is particularly common in smokers. It is now believed that early abnormalities (physiologic and biochemical) related to emphysema and chronic bronchitis may be detected at a stage when lung damage is still reversible.

- Because of the nature of these disease problems, a goal of the program is to prevent development of these diseases by early diagnosis and identification and control of risk factors.

- At the same time, because of the great number of individuals suffering from already established and progressive disease, another goal is to improve treatment and rehabilitation programs.

- Understanding the mechanisms and causes of these diseases is also an important goal and will be greatly aided by the development of basic knowledge of normal lung biochemistry, metabolism, response to injury, and repair processes. (See section on Structure and Function of the Lung.)

PROGRAM STATUS

Recent Progress. Currently, emphasis is on efforts to identify the risk factors of COPD. Cigarette smoking has long been recognized as a major risk factor for emphysema. Results from a recent cross-sectional epidemiological study indicate that smokers differ from nonsmokers in a number of respiratory symptoms and also in almost all tests of pulmonary function. Furthermore, environmental risk factors are being identified in a variety of occupations.

New lines of research have opened up through the discovery of a genetic basis for one type of emphysema. A genetic defect resulting in a deficiency of the enzyme alpha-1-antitrypsin, has been identified as a factor in the development of a severe form of familial emphysema which attacks young adults. The biological function of alpha-1-antitrypsin is to inhibit and/or prevent degradation of lung tissue elastin. This form of familial emphysema is rapidly progressive, resulting in death by the early 40's. It is not certain whether individuals with only one gene for the defect (i.e., inherited from only one parent) are also at higher risk, but early results indicate that at least one group of individuals who are carriers of the gene may be at particularly high risk.

A test has been developed that is suitable for screening populations for alpha-1-antitrypsin deficiency. Several population groups are being tested to determine the frequencies of the affected and carrier states, and to identify genetically susceptible persons who have inherited the genes for emphysema, but who have not yet developed the clinical disease. This population screening test is in the final stage of data collection, and data analysis will begin next year. Investigations are also under way to define the underlying genetic defect and to seek methods for preventing the associated emphysema.

A promising physiological method has been developed for the early detection of changes in lung function which appear to be the first sign of chronic obstructive pulmonary disease. This method, namely, measurement of closing volume (the amount of air remaining in the lungs after smaller airways collapse at the end of expiration), detects early changes in the lung which are thought to progress to signs and symptoms of COPD. It is now believed that in persons with

abnormal closing volume measurements but with otherwise normal lung function tests, progression of disease may be reversed and development of the disabling stage of the disease prevented.

Advances in understanding the structure and function of the lung (described earlier) will also be important to the eventual success in controlling chronic bronchitis and emphysema. Investigators are beginning to define the role of certain enzymes, such as elastase and collagenase, in the development of emphysema. New evidence suggests that proteolysis of lung tissue elastin rather than collagen is involved in the development of emphysema. Other studies indicate that leukocytes (white blood cells) and lung macrophages (a type of cell) may be primarily responsible for the structural damage in familial emphysema. Recent investigations have shown that a biochemical defect known as "chemotactic factor inactivator" may be associated with the lung's defense against emphysema.

Future Challenges. Progress has been made in identifying genetic factors associated with COPD. An immediate challenge is to educate people who are at risk (because of host factors) to modify their life style in order to avoid environmental exposures associated with development of COPD. Another challenge is to identify the factors in cigarette smoke that produce lung damage. Studies are planned to determine the mechanisms by which the lung clears itself of particles inhaled in cigarette smoke and how these mechanisms are modified by pollutants in the environment.

Measures to modify the smoking habits of the population need to be developed in collaboration with behavioral scientists. Particular emphasis should be placed on preventing or decreasing smoking in the young.

Host factors other than alpha-1-antitrypsin deficiency may be determinants of emphysema and chronic bronchitis. A systematic search for inherited enzyme abnormalities that predispose to development of COPD is an essential part of the program on host factors. Additional studies are to be initiated to explore detailed intrafamilial and interfamilial genotype patterns.

The promising results of genetic and biochemical studies of familial emphysema suggest the possibility of alpha-1-antitrypsin replacement therapy. Synthetic peptides which have functional effects similar to alpha-1-antitrypsin (i.e., they inhibit and/or prevent degradation of lung tissue elastin) are now available. They have been distributed to scientists who are engaged in animal studies of inhibitory mechanisms and who are evaluating the efficacy of the synthesized peptides on inhibition of elastin degradation. If effective, the use of synthetic peptides could reduce the morbidity and mortality due to emphysema.

PROGRAM PLANS

Actions. The Institute plans to:

- Expand studies addressed to early detection of emphysema and chronic bronchitis by (a) encouraging investigator-initiated research, and (b) extending targeted programs to include longitudinal studies utilizing promising techniques and devices to investigate the natural history of early emphysema and chronic bronchitis in selected populations

- Extend investigations to elucidate the roles of host factors and environmental agents in the etiology and pathogenesis of emphysema and chronic bronchitis by (a) continuing interdisciplinary programs in Specialized Centers of Research, (b) continuing targeted programs using selected populations, and (c) encouraging investigator-initiated studies.

Schedule. Present programs relating to pathophysiology and diagnosis of advanced disease will be reduced gradually through FY 80. New activities in early diagnosis, clinical trials, and multidisciplinary studies of the effects of smoking represent increased efforts through FY 80. Research on host factors will decrease in FY 76, as ongoing programs on alpha-1-antitrypsin are completed; as information on other host factors becomes available, this area will again increase in activity.

4. FIBROTIC AND IMMUNOLOGIC LUNG DISEASES

PROGRAM GOALS

Fibrotic and immunologic lung diseases result from the interaction of a variety of environmental and host factors. These lung diseases can be prevented or treated if the offending substances can be removed or their effect suppressed. A primary goal of the National Program in this area is to disseminate information (see Prevention, Control, and Education Programs) about the causes of these diseases, as these are discovered through research, and how to avoid them. The Institute's current research program on fibrotic and immunologic lung diseases focuses on asthma, pulmonary fibrosis, hypersensitivity pneumonitis, and noninfectious granulomatosis. In cases where exposure cannot be avoided or the disease prevented, effective treatment depends on understanding the processes leading to disease and minimizing their impact on the lungs.

- The research goal is to conduct fundamental investigations to provide the knowledge necessary for improved therapy.

PROGRAM STATUS

Recent Progress. Significant advances in the early detection of asthma, an immunological disease, have been achieved through the methacholine inhalation challenge technique. This test identifies individuals with asthma before it is clinically apparent.

Renewed interest in the challenge technique is providing a sound pathophysiologic basis for improved diagnosis of allergic diseases. The challenge test utilizes inhaled compounds that cause a bronchial or alveolar immunologic response. Until recently, patients were challenged with nonspecific compounds such as methacholine. But now specific antigens are used, permitting observations that have led to better understanding of the disease mechanisms in asthma and hypersensitivity pneumonitis.

Recent programs have established that cells (such as lymphocytes--a type of white blood cell) from asthmatics contain lower levels of cyclic adenylic acid than those from normal subjects. This deficiency is attributed in part to a difference in the phospholipid composition of cellular membranes in asthmatics. It has been found that restoring phospholipids to the deficient cells raises the level of cyclic adenylic acid.

Studies are being carried out on the immunologic mechanisms implicated in pulmonary disorders, including diseases which are thought to be autoimmune in origin. Patients are being studied for evidence of immunological abnormalities. Methods of studying cell-mediated immunologic responses to circulating antibodies are now being applied to lung diseases. Basic studies of connective tissue (collagen and elastin) and correlations of structure and function are in progress. Present studies include histological and electron microscopic analysis of epithelial and endothelial damage. A registry of morphological, physiological, and clinical data on patients with diffuse fibrosis is being maintained.

In March 1974, the Institute sponsored a workshop on chest radiography to identify criteria for the use of chest X-rays in epidemiologic studies of occupational lung diseases and to discuss their possible role in diagnosis of obstructive lung diseases.

Hypersensitivity pneumonitis, usually a consequence of inhaled allergens, is common among pigeon breeders, farmers, and workers exposed to detergent enzymes or epoxy resins. Recent studies recognize a number of forms of these disorders, both acute and chronic. New information is being tabulated about basic differences between ill and well individuals who have had similar exposures to environmental antigens. An interdisciplinary program has been initiated which addresses the problem of chemical mediators and their involvement with pathogenesis and pathology of these disorders.

Sarcoidosis is a systemic granulomatous disease which very frequently affects pulmonary and myocardial function. When sarcoidosis

occurs in these organ systems, morbidity is especially high. Even in its more benign forms, this disease is prevalent enough to be considered a national health problem. It has marked economic consequences because it occurs in early and middle adult life. While sarcoidosis has been recognized for many years, a major obstacle to determining its prevalence and understanding its pathogenesis has been the lack of a reliable and simple diagnostic test. Advances in technology have provided an opportunity to study cell-mediated immune processes in vitro. Recently, successful use of in vitro macrophage migration inhibition, induced by sarcoid lymph node preparations, has made it possible to study the etiology and pathogenesis of sarcoidosis without the limitation of the in vivo skin test. This opens new approaches to the diagnosis of sarcoidosis.

The Institute has recently initiated a contract program to continue development of an in vitro test for sarcoidosis and to determine the role of antigens in the etiology and pathogenesis of this disease.

Future Challenges. Where population groups are known to have a high prevalence of pulmonary fibrosis or immunologic lung diseases, epidemiological studies should be carried out to identify the factors responsible. This identification of specific etiologic agents is crucial to the development of effective control measures aimed at eliminating these factors. The Institute will seek to coordinate epidemiologic programs through use of standardized methods and protocols and increased communication, so that data can be compared.

Advances in biochemistry, pharmacology, and immunology have only recently been brought to bear on problems of lung disease. These basic scientific disciplines need to be increasingly drawn upon in the development of therapy, prevention, and control of immunologic and fibrotic lung diseases. Understanding the role of certain endogenous mediators and their composition and mechanism of action, though difficult to achieve, is essential. The specific roles in lung disease of the molecular mechanisms involved in cell-mediated and antibody-mediated immunologic responses must be defined. It is anticipated that in the future the inflammatory and bronchoconstricting responses mediated by certain hormonal agents will be better understood. The mechanisms of collagen synthesis and degradation need to be studied in order to develop therapy directed at specific events in the chain of metabolic changes leading to disease. It is anticipated that specific components of collagen will be identified and that improved methods of assaying elastin will allow better understanding of its metabolism in the lung.

Many animal models of immunologic and fibrotic lung diseases are available and represent opportunities for study of the pathogenesis of these diseases.

PROGRAM PLANS

Actions. The Institute plans to:

- Foster investigations relative to immunologic responses and other defense mechanisms of the lung involved in the development of fibrotic and immunologic lung disease by (a) expanding studies in Specialized Centers of Research, (b) encouraging development of investigator-initiated program projects involving both basic and clinical disciplines, (c) continuing targeted programs addressed to collagen and elastin synthesis and degradation, (d) initiating targeted programs to develop pharmacological agents that will modify connective tissue reactions associated with fibrotic diseases, and (e) initiating targeted programs to investigate etiologic factors in high risk population groups

- Emphasize the importance of developing animal models of fibrotic and immunologic lung diseases by (a) encouraging investigator-initiated studies, and (b) initiating targeted programs to develop animal models of specific granulomatous diseases and hypersensitivity lung diseases.

Schedule. At the biochemical level, attention continues to focus on characterizing the lung structural proteins, collagen and elastin. Programs on the synthetic and degradative processes of collagen and elastin are being implemented. Programs directed toward the development and study of an animal model for diffuse pulmonary fibrosis will be initiated. Epidemiologic studies of hypersensitivity pneumonitis and fibrotic lung disease should provide useful information on the pathogenesis and natural history of these disorders by FY 78. A recently established research and demonstration center will implement programs which will enhance some of the epidemiologic projects on fibrosis already underway at the facility. All of the action areas--multidisciplinary approaches, targeted programs, etiology and epidemiology--represent incrementally increasing activity between FY 76 and FY 81.

5. RESPIRATORY FAILURE

PROGRAM GOALS

Respiratory failure may occur in many different disorders, both acute and chronic, pulmonary and nonpulmonary. Despite considerable progress in the development of sophisticated therapy, respiratory distress syndromes (acute respiratory insufficiency) of the adult remain among the most common causes of postoperative mortality and of death related to major trauma. Because acute respiratory insufficiency is potentially reversible (if recognized early and treatment is instituted promptly), the major research emphasis at present is on the identification of predisposing factors and the investigation of improved management and treatment modalities, including evaluating the utility of therapeutic and monitoring devices.

- A major program goal is to develop improved techniques for detection of potential respiratory failure.

- A second goal is to assess the efficacy of modes of therapy used for respiratory failure and to develop and evaluate devices used for monitoring and respiratory assistance during respiratory failure.

PROGRAM STATUS

Recent Progress. Techniques and devices have been developed for detecting impending respiratory failure. A new multiple inert-gas technique has been developed that measures the uneven distribution of ventilation-perfusion in the lung. The resolution and sensitivity of this method is sufficient to identify local gas exchange abnormalities in experimental animals before these can be detected by routine pulmonary function measurements.

An educational program has been initiated to disseminate information about current techniques for early identification and treatment of acute respiratory insufficiency. (See section on Prevention, Control, and Education Programs.)

Future Challenges. The specific challenges in this area are to refine techniques for early detection of respiratory failure and to improve and evaluate techniques for therapeutic management. These challenges require particular emphasis on research into the pathogenesis of respiratory failure as well as continued research to understand better the association of the physiologic measurements and the pathologic state of the lung.

To provide more effective management, new devices need to be developed that can be easily used by physicians and allied health personnel. As these new devices and techniques are developed, their efficacy must be tested in controlled clinical trials.

Further challenges include the development and clinical evaluation of microsize, reliable, and stable electrodes for the continuous in vivo blood gas measurements of pO_2 (partial pressure of oxygen) and pCO_2 (partial pressure of carbon dioxide). The development and evaluation of new noninvasive devices and techniques are required to validate the therapeutic measures commonly used for intensive respiratory care. The promising new technique to continuously measure the ventilation-perfusion ratio requires further testing. In addition, new and innovative techniques of lung imagery could contribute to the monitoring of lung function.

Despite the fact that respiratory support with positive pressure and high oxygen concentrations is widely used for therapy during respiratory failure, the long-term effects on the lung of high oxygen concentrations and continuous mechanical ventilation are still not

well understood. Further studies are needed on the effects of long-term ventilation, with and without positive pressure.

PROGRAM PLANS

Actions. The Institute plans to:

- Expand programs addressed to development and evaluation of physiologic changes associated with respiratory failure by (a) encouraging investigator-initiated studies, (b) continuing targeted programs on devices to measure blood gases, and (c) extending targeted programs to include testing and evaluation of devices to monitor other aspects of pulmonary function

- Foster investigations on improved management and treatment of patients in chronic or acute respiratory failure by (a) continuing targeted programs on development and evaluation of extracorporeal membrane oxygenators, (b) extending investigations in Specialized Centers of Research on use of ventilatory assistance, and (c) initiating targeted programs for the critical assessment of promising modes of ventilatory assistance.

Schedule. During the coming year, several programs in Respiratory Failure will be completed and a number of new programs initiated. The development of a lightweight, sensitive, and reliable respiratory gas mass spectrometer will be completed and clinically evaluated. Likewise, the design, fabrication, and feasibility testing of two new types of continuous in vivo blood gas sensors will be completed. The clinical use of the continuous ventilation-perfusion technique will be evaluated.

In addition, a program to clinically evaluate new invasive and non-invasive blood gas sensors will be initiated, as will a new program to investigate the pathologic condition of patients with respiratory failure. Program development will subsequently continue to increase gradually through FY 79. The primary emphasis will be on providing improved diagnostic and monitoring capabilities through better understanding of the pathogenesis and pathology of respiratory failure.

6. PULMONARY VASCULAR DISEASES

PROGRAM GOALS

Pulmonary vascular diseases, which include cor pulmonale (heart disease resulting from disease of the lungs or blood vessels in the lungs), pulmonary hypertension, and pulmonary edema, are serious lung disorders with often devastating consequences. Reliable data on incidence and prevalence of pulmonary vascular diseases, or on the effectiveness of present modes of therapy, are not available.

This is largely because present methods for their diagnosis and assessment of therapeutic progress involve procedures that cannot readily be used on the very ill or on large numbers of patients. These diseases could be treated if they could be identified reliably and early in their course. If simple techniques that could be used repeatedly without undue discomfort to the patient were available, the course of these disorders and the long-term benefits of therapy could be studied. The causes and development of these diseases need to be investigated through interdisciplinary studies in animal models.

- A major goal is to stimulate development of reliable, noninvasive techniques for assessing the ventricular hypertrophy associated with cor pulmonale, and for diagnosing pulmonary hypertension without the need for cardiac catheterization.

- A second goal is to encourage development of animal models of cor pulmonale and pulmonary hypertension to be used in the investigation of pathogenetic mechanisms of these diseases.

- A third goal is to foster multidisciplinary studies aimed at understanding the dynamics of fluid, electrolyte, and protein exchange in pulmonary edema.

PROGRAM STATUS

Recent Progress. Prototype techniques have been developed to study early water accumulation in pulmonary edema. The measurement of abnormal accumulation of lung water, by using insoluble inhaled gases, is noninvasive and may be performed in acutely dyspneic patients. This new approach is now at the stage of clinical evaluation. A technique utilizing thoracic impedance to determine lung water content is being developed further. Models to study the role of the pulmonary arterial, venous, and lymphatic circulations in edemic lungs are available. Animal models of pulmonary edema that simulate several clinical forms of the disease have been induced by drugs, endotoxin, hypoxia, and other mechanisms.

Basic research into the regulation of the pulmonary circulation and studies of the ultrastructural and biochemical aspects of vascular smooth muscle have been initiated. There are currently more than ten humoral substances known to affect the pulmonary circulation (by raising or lowering pulmonary artery pressure). For each of these, there exist specific pharmacologic substances which can moderate their actions, for example, histamine and antihistamines, adrenaline and alpha- and beta-adrenergic blocking agents, prostaglandins, and aspirin. Investigators are now studying the role of each of these substances in the regulation of pulmonary artery pressure.

Future Challenges. Pressing needs include the development of techniques for early diagnosis, and the evaluation of the efficacy of therapy by serial assessments of the patient's condition over long periods. Both of these needs depend upon development of reliable techniques that are noninvasive, safe, and cause minimal discomfort to the patient. The noninvasive techniques already developed do not meet the clinical needs for diagnosing and screening for pulmonary hypertension, cor pulmonale, or pulmonary edema.

A major challenge is to develop diagnostic techniques that would make it possible to screen large numbers of persons and identify population groups for the study of etiologic factors, pathogenetic mechanisms, and for assessment of therapeutic regimens.

With an expanded basic research effort, scientists will be able to determine the significance and role of each of the many humoral substances which affect the pulmonary circulation. With adequate capability for detecting and measuring early and small abnormalities in the pulmonary circulation coupled with knowledge of the significance of humoral mediators, it will be possible to employ specific pharmacologic substances to modify pulmonary artery pressure. Assessment of this therapy on the course of pulmonary hypertension will then be possible.

New and better animal models are needed to study the pathogenesis and pathophysiology of cor pulmonale and pulmonary hypertension at the molecular and biochemical levels, and to assess diagnostic and therapeutic techniques. Available animal models do not adequately represent the disease process as it occurs in humans.

PROGRAM PLANS

Actions. The Institute plans to:

- Foster fundamental studies of pulmonary vascular diseases by encouraging investigator-initiated research in (a) the edematous lung including the dynamics of exchange of water, protein, and electrolytes, and the biochemistry of edema fluid, and (b) the pulmonary smooth muscle vasculature, with particular emphasis on changes associated with development of pulmonary hypertension and the role of vasoactive amines

- Initiate targeted programs addressed to development and evaluation of safe, noninvasive devices for detecting and monitoring changes associated with cor pulmonale, pulmonary hypertension, and pulmonary edema

- Initiate targeted programs to develop animal models of cor pulmonale, pulmonary hypertension, and pulmonary edema.

Schedule. The Institute plans to place special emphasis on the area of pulmonary vascular diseases in its new Specialized Centers of Research announcements. In addition, specific initiatives will be undertaken to foster development of noninvasive methods for assessing pulmonary hypertension and cor pulmonale. A workshop to keynote the problems of pulmonary hypertension and cor pulmonale is planned.

7. INHALATION DISEASES

PROGRAM GOALS

This program is addressed to respiratory diseases that result from the direct effects of inhaled dusts, vapors, or gases and which can be prevented by removal of the offending substances or by protecting individuals from them. Therefore, a primary goal of the National Program is to disseminate information about the causes of these diseases and how to avoid them. (See section on Prevention, Control, and Education Programs.)

- The research goal is to improve identification of the specific causes of these diseases and thereby prevent their development.

PROGRAM STATUS

Recent Progress. Epidemiologic projects have focused on specific industrial airborne substances implicated in pulmonary disease and identification of the etiologic agents.

A relationship between cumulative exposure to asbestos dust and radiographic opacities in the lung (pulmonary asbestosis) has been demonstrated.

Studies on exposure to toluene di-isocyanate (TDI) dust in a new manufacturing plant have provided information on physiologic pulmonary impairment in exposed workers, on the type of immune response produced, and on factors associated with clinical manifestations of the impairment. These data have provided information on TDI dose-response relationships and can aid in the identification of individuals who can be expected to have an adverse respiratory response after exposure to TDI.

Future Challenges. Previously, the pneumoconioses were thought to be limited to certain jobs in specific occupations. But it is now recognized that not only are those workers potentially at risk, but also their co-workers and, in some cases, the community at large. This possibility gives the problem even greater importance in terms of national health. The major challenge is to reduce or prevent exposure to hazardous substances.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue current programs to improve the detection, relief, and prevention of inhalation diseases.

Schedule. In the coming year, the Institute's program on Inhalation Diseases will be incorporated into other appropriate lung disease program areas.

8. RESPIRATORY ASSISTANCE

PROGRAM GOALS

Because respiratory failure is a debilitating and often fatal disorder that may be an eventual complication of nearly every respiratory disease, the development of effective therapeutic devices to provide respiratory assistance is of the greatest importance.

- The major goal of this program is to apply new technology to the treatment of respiratory failure and to develop improved rehabilitative devices and techniques.

PROGRAM STATUS

Recent Progress. Major progress in this program area has been in the development and testing of membrane oxygenators in animals and in man. These oxygenators have demonstrated sufficient promise to warrant initiation of a collaborative clinical trial involving nine intensive care centers. These centers will evaluate, under controlled conditions, the efficacy of managing acute respiratory failure by respiratory care that includes the use of a membrane oxygenator.

A lung pathology center will be established to analyze material obtained from patients in respiratory failure. Light and electron microscopy will be used to correlate lung pathology with the treatment modality.

The therapeutic importance of oxygen inhalation devices for patients in respiratory failure is established. However, elevated concentrations of inspired oxygen have been found to be potentially dangerous. Animals as well as humans show effects of tracheobronchitis and a marked depression of mucus clearance after prolonged exposure to high concentrations of oxygen. Studies of the cellular aspects of oxygen toxicity have shown that damage to the Type II cell may interfere with lung repair by cellular division.

Future Challenges. An immediate need, if prompt respiratory assistance is to be provided, is the clinical determination of which patients in respiratory distress may benefit from long-term (days)

membrane oxygenator support and when in the course of their distress such support should be administered. Suitable criteria could provide much needed direction for effective clinical use of this new support device and allow maximum exploitation of its potentialities.

Continued development of artificial lung systems is anticipated. Techniques of blood management required by currently available membrane oxygenators preclude their use in many patients who require respiratory assistance (for example, where bleeding is severe). New approaches and materials could lead to systems of greater clinical utility. The testing of new oxygenator materials may lead to a device which requires less complex blood management during clinical use.

To provide more effective respiratory assistance, further research is required into the pathogenic mechanisms producing hypoxemia, and the influence of routine and new treatment modalities upon these pathologic processes.

PROGRAM PLANS

Actions. The Institute plans to:

- Extend programs addressed to ventilatory-assist devices and oxygenators to insure improvements in available devices and development of new ones
- Test presently available and promising new devices in controlled clinical studies
- Investigate the influence of treatment modality on lung pathology
- Continue and extend the Specialized Centers of Research, where sophisticated techniques are available, in order to capitalize on what is known and to improve present modes of therapy.

Schedule. A collaborative program involving nine centers has been initiated to establish the clinical criteria for the therapeutic use of membrane oxygenators in the management of acute respiratory failure. A program will be initiated this year to analyze pathologic lung material from these patients and correlate the pathologic data with the treatment modality. In addition, design, fabrication, and feasibility studies for several new and novel oxygenator designs will be completed. Analysis and monitoring of other forms of respiratory assistance devices will continue to be increased in subsequent years, reaching a peak by FY 78.

In the coming year, the Institute's program in Respiratory Assistance will be incorporated into its Respiratory Failure Program.

PREVENTION, CONTROL, AND EDUCATION PROGRAMS

This is a new program area in Lung Diseases; the first year of activity is represented by the several initiatives detailed below.

1. NATIONAL RESEARCH AND DEMONSTRATION CENTERS

The first National Research and Demonstration Center in lung diseases was funded in December 1974 at the University of Vermont in Burlington. The Center will coordinate the activities of several groups, including the State Department of Health, the Vermont Lung Association, and members of the Departments of Community Medicine, Continuing Medical Education, Medicine, Pathology, and Physiology of the University of Vermont School of Medicine.

The Center will act as a prototype system for training, education, treatment, and prevention in the field of respiratory disease. Specific activity and targets include: (1) an interdisciplinary study of the prevention and control of pneumoconiosis, (2) research in the pathology and management of acute pulmonary trauma, in basic methodology of computer-assisted instruction in pulmonary physiology, in the pathology, pathogenesis, biochemistry, immunology, and cell physiology of diffuse interstitial lung disease, (3) clinical demonstrations and applications of research findings of lung disease using a problem-oriented medical information system, (4) demonstration of regional management of specified lung disease problems utilizing an interhospital computer network, (5) demonstration of graduate and postgraduate educational methodology using audiovisual aids and regional interactive television, (6) dissemination of information to the public relating to lung disease problems specified by the regional Lung Disease Management Committee, and (7) provision of a broadly based multidisciplinary training environment for the undergraduate, graduate, and postgraduate scientists and health professionals in research, clinical practice, teaching, and continuing education related to the etiology, prevention, diagnosis, and treatment of diseases of the lung.

The majority of the basic and clinical research activities related to the Center's goals are supported by a Specialized Center of Research grant.

2. EDUCATIONAL PROGRAMS

The Institute is initiating a major effort to improve the skills of health care providers in the treatment and prevention of respiratory disease. The development and evaluation of educational programs designed to reach various target groups is central to this effort. One program is now underway, one has been announced, and one is in the planning stage.

Actions. The Institute Plans to:

- Continue educational programs addressed to community physicians, nurses, midwives, and allied health personnel involved in the care of neonates, to provide information about early recognition and prompt treatment of hyaline membrane disease

- Continue educational programs concerned with early recognition and prompt treatment of respiratory insufficiency.

Three projects are underway to develop educational programs for early treatment of acute respiratory insufficiency. These will be designed for professional and nonprofessional personnel who are likely to be the first contacts of patients suffering from acute respiratory insufficiency. The programs will train these persons to recognize this disorder and initiate early treatment with well-accepted therapeutic procedures. The goal of the effort is to reduce morbidity and mortality from acute respiratory insufficiency. The investigators will bring both innovative and well-established educational methodology to bear on effective dissemination of information. Three different approaches will be used, and a common scheme for evaluation will be followed so that the relative effectiveness of each approach can be determined.

The Institute has published a request for proposals for development and evaluation of educational programs dealing with the recognition and early treatment of neonatal respiratory insufficiency and respiratory failure. Respiratory failure is at present the most common cause of death in the newborn. It can be prevented if respiratory insufficiency can be anticipated or recognized at onset, and effective therapeutic measures are promptly instituted. To accomplish these ends, it is necessary to identify infants likely to be at risk so that local resources can be mobilized in advance for their proper care. To identify such infants, it is necessary to recognize prenatal and perinatal conditions in the mother which are likely to lead to respiratory problems in the neonate or to prematurity, which is frequently associated with neonatal respiratory distress syndrome (hyaline membrane disease). The education programs which the Institute wishes to establish will be directed to physicians, nurses, physicians' assistants, midwives, and other professionals involved in prenatal care, delivery, and neonatal care. It is anticipated that an effectively designed and executed program which will provide information on how to recognize these disorders and initiate early treatment with accepted therapeutic procedures will help to reduce both mortality and morbidity in the neonate. The programs will be designed for application in geographic areas and community settings where intensive care facilities for the neonate are not readily available.

The Institute is planning to develop computer-assisted instruction programs in pulmonary education. The goal of this effort will be the improvement of educational materials and methodology for teaching pulmonary physiology and pathology to undergraduate medical students and the updating of skills and knowledge of nonspecialist, practicing physicians in the field of prevention, control, and treatment of respiratory disease.

PROGRAM COORDINATION

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 stresses the establishment of an Interagency Technical Committee (IATC) that ". . . shall be responsible for coordinating those aspects of all Federal health programs and activities relating to . . . lung . . . to provide for the full communication and exchange of information . . . ." This committee, consequently, provides a forum for representatives from diverse Federal backgrounds to discuss programs of mutual interest in lung diseases. A formal presentation of the Institutes' programs in lung diseases was given at the Interagency Technical Committee's fifth meeting on June 14, 1974. This presentation identified activities in which collaboration with other Federal agencies is presently underway.

Highlights of these major cooperative programs are presented below.

- Pneumoconioses (Black Lung). Because coal miners are at high risk of developing respiratory diseases from exposure to airborne dusts, a joint committee, the Working Party on Respiratory Diseases Among Coal Miners, has been established, at the request of the Governor of Pennsylvania, to define the types of efforts most urgently required to prevent or treat work-related respiratory diseases. This committee has members from Federal (National Institute for Occupational Safety and Health, National Institute of Environmental Health Science, U.S. Bureau of Mines, and National Heart and Lung Institute); State (Commonwealth of Pennsylvania); nonprofit (American Lung Association); industry (U.S. Steel and others); and university organizations.

  The Working Party has four subcommittees: (1) Subcommittee on Clinical Problems with the charge to develop an optimal management program, develop simple tests for diagnosis and effectiveness of therapy, and develop specific graduate educational and physician education programs; (2) Subcommittee on Research Perspectives in Epidemiology and Small Airway Disease, with the charge to study small airway disease in coal workers and investigate the epidemiology of coal workers' respiratory disease; (3) Subcommittee on Research in Pneumoconiosis, with the charge to study the ultramicroscopic particles in relation to the problem and investigate the inactivation of dust in the lungs; (4) Subcommittee on Prevention and Treatment of Coal Workers' Respiratory Diseases, with the charge to investigate the pathogenesis of progressive massive fibrosis and the cellular biology approach to the problem. Though there have been changes during the past year in the administration of this cooperative program, the Governor of Pennsylvania has expressed renewed interest to continue the Working Groups. A reassessment and evaluation of committee reports and the implementation of new activities are planned for this year.

- Emphysema and Chronic Bronchitis. A conference sponsored jointly by the Institute and the American Thoracic Society was held last

year to review the available data on tests of lung function, to determine whether such tests are suitable for mass population screening programs, and whether alterations in lung function tests can be correlated with structural changes in lung tissue.

- Smoking. Cooperative efforts to reduce smoking and its harmful effects on health are being conducted with the National Clearinghouse for Smoking and Health, Center for Disease Control. The goals are to study smoking behavior and its modification, and to utilize these findings to develop an intervention program for the general population. A Comprehensive Smoking Withdrawal Program, part of this cooperative effort, will conduct a research and demonstration project to develop a community-based, comprehensive control program that can provide services to individuals on a referral basis, as well as to industry, and civic and community organizations.

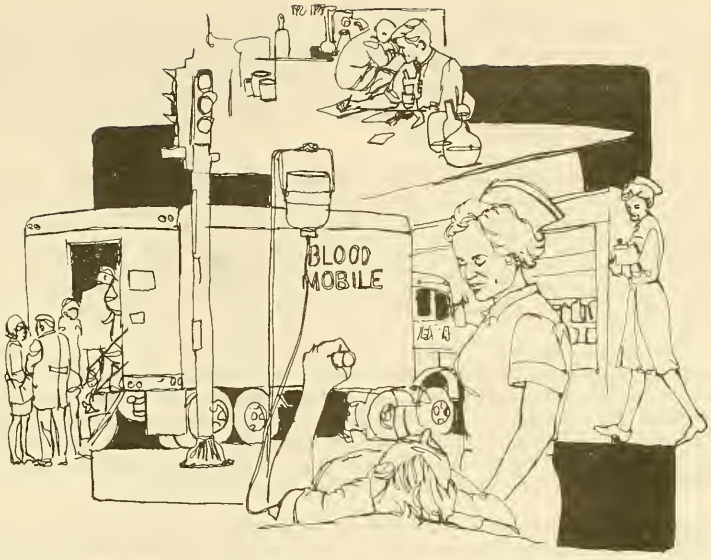
- Manpower Development. The NHLI collaborates with the American Thoracic Society and the American College of Chest Physicians in surveying the national needs for research and manpower development in pulmonary diseases. The Institute is also coordinating activities in this area with the American Lung Association and other voluntary organizations interested in the implementation of the National Program.

MANPOWER RESOURCES

A survey of professional manpower has revealed that 130 currently funded but unfilled vacancies exist on medical school faculties in lung diseases and at least 20 additional vacancies exist at research institutes. It is estimated that, within the next two to three years, approximately 550 well-trained individuals will be required for the staffs of medical schools and research institutions engaged in lung disease related activities.

Research in the pulmonary disease area has now developed special and almost unique requirements. Increasingly, it has become possible to study lung diseases by investigation of underlying mechanisms, and physicians and scientists must now draw upon fundamental disciplines that are comparatively new to the lung field, such as biochemistry, cell biology, immunology, and bioengineering.

Because of the great need for interdisciplinary research and training in the lung diseases area, the Institute plans to give high priority to such programs. To date, basic scientists have not been conversant with the problems of lung diseases, and pulmonary clinicians have been generally uninformed about the basic studies that might contribute to their research. The Institute believes that for these special interdisciplinary research training programs, where new and basic contributions can be made, between 150 and 200 research fellows should be supported in the immediate future.



BLOOD DISEASES AND BLOOD RESOURCES

The plans for developing the Institute's program in blood diseases and blood resources as well as for coordinating the National Program in this area were outlined in the National Heart and Lung Institute Summary (Volume I) of the National Heart, Blood Vessel, Lung, and Blood Program on May 1, 1973. The First Annual Report of the Director of the National Heart and Lung Institute on February 13, 1974, presented a review and assessment of the Institute's activities in the field of blood diseases and blood resources and a revised Program Plan for the next five years. This second annual report deals with four areas in blood diseases and blood resources:

1. Bleeding and Clotting Disorders
2. Biomaterials
3. Sickle Cell Disease and Other Disorders of the Red Blood Cell
4. Blood Resources.

The Institute seeks to carry out a comprehensive program including fundamental and clinical research, professional development and training to fill projected needs, and education, prevention, and control activities to assure orderly

application of the knowledge gained through research. In developing and supporting its programs in blood, the Institute seeks to use all available support mechanisms as appropriate. These include investigator-initiated research projects, program project grants, goal-oriented centers such as the Specialized Centers of Research (SCORs), a National Research and Demonstration Center, and targeted research and development contracts. The Institute also supports an intramural research program.

The National Program embraces a number of research, prevention, and education areas where interorganizational coordination is vital if effective national efforts are to succeed. The Institute also plays a key role in a number of collaborative efforts with other agencies and organizations seeking to help coordinate the many activities related to its mission. Examples of the coordination activities in blood diseases and blood resources include those in sickle cell disease, Cooley's anemia, hemophilia, hepatitis, and management of blood resources.

This year's report continues to update and review the Institute's program goals, progress, actions, and schedules. The recent progress and future challenges identified by the Institute, its advisors, and the scientific community are presented and the updated Program Plan for the next five years is described. Future reports will reflect input from the Blood Diseases and Resources Advisory Committee which has recently been chartered (October 1974).

Before discussing the scientific aspects of the National Program in Blood Diseases and Blood Resources, a summary description is presented (in italics) of the blood and the major problem areas within the National Program.

DEFINITIONS OF MAJOR PROBLEM AREAS

This section provides a framework in nontechnical language to help the nonspecialist understand the subsequent discussions of specific blood diseases and blood resources programs. It summarizes:

1. *The blood: Its components and functions*
2. *Major problem areas.*

1. THE BLOOD: ITS COMPONENTS AND FUNCTIONS

Blood consists of a number of formed elements suspended in a fluid called plasma. The formed elements are erythrocytes or red blood cells, leukocytes or white blood cells, and thrombocytes or platelets (see Figure 8). Blood is a vital component of the circulatory system since it is the vehicle in which oxygen, nutrients, and other chemicals are carried via the blood vessels to every part of the body, to be exchanged for carbon dioxide and waste products which in turn are transported away by the blood.

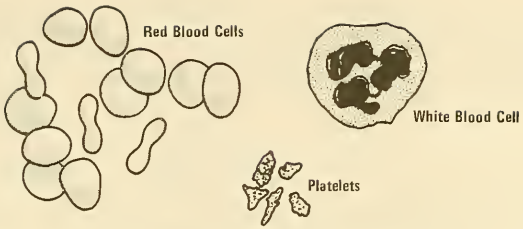


Figure 8. Formed Elements of the Blood

Plasma contains numerous materials which include proteins, carbohydrates, lipids, electrolytes, and hormones. The proteins include albumin, globulin, fibrinogen, and several other clotting factors (see Figure 9). Plasma proteins play important roles in body functions since they participate in nutrition, coagulation, acid-base regulation, and immunological responses. In addition, they contribute to the osmotic pressure, viscosity, and suspension characteristics of the plasma.

Erythrocytes, or red blood cells, have as their major function the transport of oxygen and carbon dioxide. The red cell is equipped to release its oxygen to the tissues rapidly and to take up carbon dioxide from the tissues. The hemoglobin pigments are essential components of the red blood cell and play vital roles in the transport of oxygen and carbon dioxide in the blood as well as in the rapid exchange of carbon dioxide and oxygen in the lungs and in the tissues.

Leukocytes, or white blood cells, protect the body against infection.

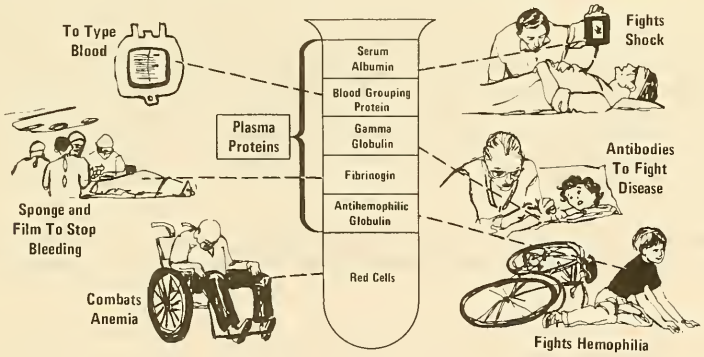


Figure 9. Common Blood Fractions and Some of Their Medical Uses

Thrombocytes, or platelets, are small, colorless discs that play an important role in the arrest of bleeding by adhering to cut surfaces and aggregating into clumps. In this way they help plug the holes in the blood vessel walls. They also provide a protein which accelerates the formation of a fibrin clot.

2. MAJOR PROBLEM AREAS

The Institute's programs in blood diseases focus on bleeding and clotting disorders related to the platelets and components of blood plasma such as clotting factors, including antihemophilic factors, and on red cell disorders, particularly those related to hemoglobin, the red cell membrane, and its metabolic machinery. In the case of the biomaterials program, the principal concern is the interaction of blood with artificial surfaces and ways to optimize implant materials to prevent clotting and damage to any of the components of the blood. In the blood resources program, the Institute is concerned with all constituents of blood in their roles as therapeutic agents and in the management of blood resources.

The following paragraphs summarize the four major problem areas in blood diseases and blood resources within the National Program.

Bleeding and Clotting Disorders

Before describing the major bleeding and clotting disorders addressed in the National Program, the general principles involved in the arrest of bleeding (hemostasis) are outlined below. The hemostatic mechanism is designed to repair breaks in the wall of small blood vessels, namely the components of the microcirculation. The microcirculation is an important part of the circulatory system. It carries to the cells of the body the materials needed for their metabolism and function and removes their waste products so that the internal environment is maintained in a manner which allows the cells to survive and perform their interrelated tasks. Bleeding and clotting in the microcirculation contribute to the adverse effects of many diseases and disorders such as hypertension, stroke, diabetes, infectious and inflammatory disease, autoimmune disease, host-graft rejection, cancer, sickle cell anemia, drug toxicity, mismatched blood transfusion, liver disease, and nephritis. The impact of the bleeding and clotting diseases is vast even if it cannot be expressed statistically.

The diagram below, Figure 10, is a simplified representation of some of the complex events known to be important in hemostasis or arrest of bleeding.

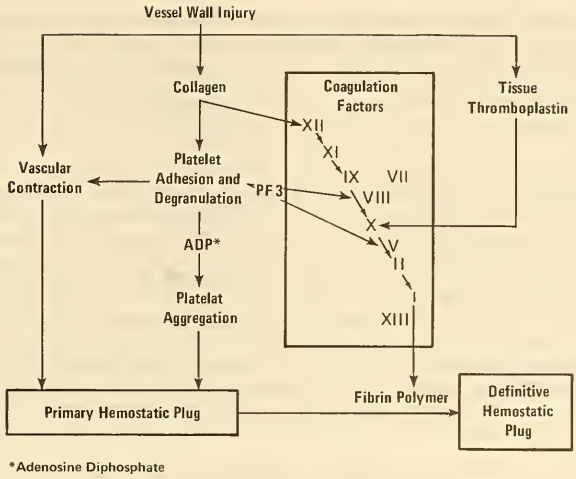


Figure 10. Simplified Representation of Events in Hemostasis (Blood Clotting)

Simply stated, the hemostatic sequence involves the following steps:

- *First, blood escapes from the injured blood vessel resulting in a decrease of blood pressure inside the vessel. This sets in motion a complex chain of reflexes which cause the vessel to constrict.*

- *Second, platelets rapidly (within one to two seconds) adhere to the irregularity in the injured vessel wall. The platelets initially attracted to the irregular site swell and release components which act as chemical messengers causing other platelets in the area to become sticky and adhere to the injured blood vessel wall. As more platelets aggregate, a temporary platelet plug is formed which achieves primary hemostasis.*

- *Third, as a result of the vascular injury and platelet changes, the coagulation mechanism is initiated. In a complex series of steps, a soluble component of the plasma (fibrinogen) is turned into fibrin (an insoluble protein) which forms the essential portion of the blood clot (see Figure 10).*

- *Fourth, clot formation is limited to prevent occlusion of the vessel; the clot contracts to seal the lesion; and after healing has occurred, the clot is dissolved by proteolytic enzymes.*

This oversimplified description of the events involved in the arrest of bleeding offers a framework for understanding how the blood vessel wall, platelets, and coagulation mechanisms are interrelated. It is important to remember that the vascular and platelet mechanisms act to achieve immediate (primary) hemostasis, and that blood coagulation is a later event (secondary hemostasis) that acts to reinforce and replace the temporary platelet plug.

Bleeding Disorders. A deficiency of hemostasis (i.e., a tendency toward bleeding) may result from a shortage of any of the plasma components required for clotting. These shortages may arise in a variety of ways. For example, since fibrinogen, prothrombin, and some other blood coagulation factors are formed in the liver, liver diseases which alter prothrombin or fibrinogen synthesis can result in excess bleeding. Excessive blood loss is a major cause of death and morbidity in a variety of circumstances such as after severe injury, after surgery, in leukemia, and in liver disease. The threat of hemorrhage limits the aggressive management of some forms of cancer. The classical hereditary condition of hemophilia results from the absence of, or deficiency in, antihemophilic factors. Bleeding into organs and tissues may impair or destroy their function and uncontrolled external blood loss may result in death.

The hemophilias are sex-linked diseases occurring almost exclusively in males. Although the known hemophilic population of this country is only about 25,000, hemophilia constitutes a major national health problem for two reasons. First, treatment must be continued throughout the lifetime of the patient at enormous cost (the current yearly cost to replace the missing clotting factor alone is estimated to be in excess of $6,000 per patient, or more than $120 million for the 80 percent of hemophiliacs who can benefit from this factor). Second, treatment of the disease presents one of the largest single demands upon the nation's blood resources.

Clotting Disorders. Thromboembolic disorders can result from one of several coagulation abnormalities including: (1) presence of considerable disease of the blood vessel walls; (2) stagnation of blood flow; and (3) deficiency of naturally occurring anticoagulants within the blood. The clot which remains fixed at the initial site of injury in the blood vessel wall is called a thrombus, and the resulting condition is called thrombosis. As blood flows past the thrombus, fragments (emboli) may break loose and circulate through the vascular system. An embolus continues to circulate until it reaches a vessel too narrow for its passage; it then becomes lodged in the blood vessel thereby occluding it. Clotting in the arteries deprives a part of the body of its blood supply; clotting in the veins impedes the return of blood to the heart. When excessive clotting affects small blood vessels and capillaries (collectively termed the microcirculation), tissues and cells cannot function well because they are deprived of essential oxygen, energy, regulating hormones and building blocks, and noxious waste products cannot be removed effectively.

The consequences of abnormal clotting depend on the organ or region of the body in which it occurs. In vessels of the heart, brain, lung, or other vital organs, the result can be catastrophic; in less vital areas, the effects may be mild and transitory. With time, the body's clot-dissolving mechanism restores the

integrity of the circulation. However, the speed of this process is insufficient in the case of vital organs where even a very brief interruption of blood supply may result in irretrievable loss of function or death of tissue.

The impact of abnormal clotting is considerable. Arterial thrombosis causes or complicates a variety of diseases in all parts of the body; for example, thrombosis in the coronary arteries contributes to heart attacks, thrombosis involving the vessels of the kidney contributes to kidney failure, and arterial thrombosis and cerebral hemorrhage play major roles in stroke. Thrombosis in the veins may produce pulmonary embolism; that is, clot fragments may be carried in the blood from their site of origin to the lungs. Clotting in the venous circulation complicates many illnesses and surgical procedures. Autopsy studies show evidence of venous thrombosis in about 50 percent of cases examined, regardless of cause of death, and fatal pulmonary embolism may complicate as many as 1 in every 1,000 major surgical procedures.

Thrombosis induced by contact of the blood with foreign surfaces remains the major unsolved problem in the development of artificial organs and prosthetic vessels or devices that temporarily assist the circulation.

Biomaterials

Biomaterials are synthetic materials which can be implanted in the body and used in a variety of medical devices. To be "blood compatible," such materials must not cause damage to the various components of blood and must not induce blood to clot. In addition, biomaterials must possess specific properties suitable for specialized functions (for example, gas permeability for oxygenation devices) and have minimal risk of causing chemical toxicity, allergic reactions, and tumors. Several approaches are being pursued in the development of suitable biomaterials. Properties of the vessel wall have been imitated by "hydrogels," a network structure of long polymer chains and water. Blood compatible surfaces can be grafted or bonded to a variety of materials which have otherwise promising physical properties. Another approach involves the use of human cells which can be grown in culture and attached to certain man-made materials to make them compatible with blood. Materials can be synthesized which contain anticoagulants, clot-dissolving enzymes, and surface-active agents. Composite materials can be produced which are based on a variety of components mentioned above.

Sickle Cell Disease and Other Disorders of the Red Blood Cell

The three groups of disorders considered here include sickle cell anemia and sickle cell trait, conditions closely related to sickle cell disease such as Cooley's anemia, and defects affecting the red blood cell membrane and its metabolic machinery.

Sickle Cell Anemia and Sickle Cell Trait. Sickle cell trait, the most common inherited blood abnormality in the United States, is believed to be carried by more than 2 million U.S. citizens, primarily blacks. However, most of these

"carriers" are healthy. If two carriers marry, each of their children has a one in four chance of having sickle cell anemia, a painful and debilitating disorder affecting nearly 50,000 individuals (see Figure 11). About one in 500 black babies in this country is born with sickle cell anemia.

Sickle cell anemia is a disorder characterized by the presence of painful "crises" which may last for hours or days, a chronic anemia related to accelerated destruction of red blood cells and acute and chronic damage to various body organs. These clinical manifestations are caused by the presence of an abnormal hemoglobin (Hb S) leading to crescent shaped "sickled" red cells. Sickled red cells have difficulty traversing the small blood vessels and tend to occlude them. This in turn results in impaired circulation, tissue damage, and painful crises.

Sickle cell anemia, the homozygous state for the gene for Hb S (S/S disease), often causes severe and disabling symptoms and may markedly shorten life. Milder symptoms and greater longevity are encountered in certain genetic variants of sickle cell disease (Hb S-C disease, Hb S-thalassemia).

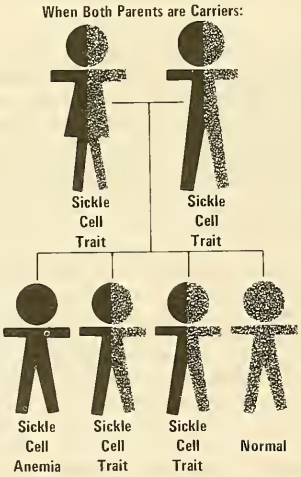


Figure 11. Hereditary Impact of Sickle Cell Trait

If sickling of the red cells could be altered or prevented, perhaps by a suitably designed pharmacologic agent, both the quality and duration of life for patients with sickle cell disease would be greatly improved. While we know the primary defect in sickle cell disease (a mutation which leads to the substitution of a single amino acid in one of the two kinds of polypeptide chains in

hemoglobin), much remains to be learned about the formation and structure of the aggregates of deoxygenated Hb S and the interactions of these polymers of Hb S with other red cell components. In a sense, the molecular and cellular manifestations can be considered "causes" of sickle cell disease, since the clinical manifestations are based upon the molecular and cellular phenomena.

The cost of caring for a patient with sickle cell disease may approach $2,500 to $5,000 a year. The loss of time from school and jobs, and the resultant psychological and educational problems, make this disorder one of high social and economic impact.

Cooley's Anemia. Cooley's anemia (thalassemia) results from defective production of one of the sub-units of the hemoglobin molecule, leading to rapid destruction of the red cells. It occurs in perhaps 5,000 Americans, largely of Mediterranean ancestry. Its victims suffer profound anemia and require repeated blood transfusions for survival. As with the sickle cell trait, most carriers do not have symptoms, but one in four offspring may be affected if two carriers marry.

Membrane and Enzyme Defects. Defects in red cell membranes and red cell enzymes also produce anemia by causing premature destruction of the red blood cells. Such defects are relatively rare, except one, called glucose-6-phosphate dehydrogenase (G6PD) deficiency, which occurs in about 10 percent of black males and less frequently in males of Mediterranean ancestry and other populations. Most of these individuals are healthy, but may develop anemia with certain illnesses or if they take a variety of commonly used drugs.

Blood Resources

Safe and adequate supplies of blood must be available for the nation. Most whole blood is collected by an assemblage of organizations which might be referred to as the blood service complex. As stated earlier, whole blood contains red blood cells, white blood cells, and platelets suspended in plasma. About 9 million units of whole blood and another 8.5 million unit equivalents of blood plasma are collected and used for therapy in the United States each year. The optimal management and utilization of this national resource is vital to the improved health care of the nation.

Transfusion of red blood cells is important in restoring the normal oxygen-carrying capacity of the blood in patients acutely anemic as a result of hemorrhage or chronically anemic because of diseases interfering with normal red cell production. Of all the blood components used in transfusion therapy, red cells are needed in the greatest quantity. White blood cells are vital to the body's defense against infection. In cancer, leukemia, and certain allergic states, circulating leukocytes (a type of white blood cell) are frequently diminished in quantity or impaired in functional quality. As a result, the patient is susceptible to serious infections that may not respond to antibiotic treatment. Transfusions of white blood cells may be beneficial in such cases. Platelets play a prominent role in the initiation of coagulation and in the maintenance

of the blood vessel integrity. Leukemia patients often have low circulating platelet levels, either as a result of the disease itself or as a toxic reaction to the drugs used in treating their disease. Drug treatment of solid tumors also frequently reduces platelet levels. Such platelet deficiencies can result in serious, often fatal hemorrhage. Platelet transfusions are vital for these patients.

Approximately 1.7 million liters of plasma are collected each year, mainly for the preparation of plasma protein fractions such as serum albumin used to treat shock; blood grouping protein needed for blood typing; gamma globulin for antibodies to fight disease; and antihemophilic globulin to allay bleeding in hemophiliacs.

RESEARCH PROGRAMS

The research on Blood Diseases and Blood Resources within the National Program seeks to be responsive to the legislative act which specifies ". . . studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country . . . ."

1. BLEEDING AND CLOTTING DISORDERS

Disorders of blood coagulation are a major cause of death and disability in the United States. The National Program addresses two important research areas: The hemophilias and other hemorrhagic disorders, and the thromboembolic disorders.

The Hemophilias

PROGRAM GOALS

The hemophilias are a family of genetically transmitted bleeding disorders in which blood does not clot normally. An individual with hemophilia is subject to spontaneous life-threatening bleeding episodes which can, however, be managed by prompt replacement of the missing or inactive clotting factor. As a result of significant advances in research, the outlook for the hemophiliac has changed substantially over the last two decades.

- The major long-term research goals are to understand better the genetic and pathologic mechanisms underlying bleeding disorders.
- The immediate goals are to develop improved diagnostic techniques and specific treatments for hemorrhagic disorders.

PROGRAM STATUS

Recent Progress. Specific clotting factors lacking or inactive in the hemophiliac have been identified, partially characterized, and can now be separated commercially from normal donor plasma. These research advances, coupled with a more sophisticated management of our national blood resource, promise to make better products for the treatment of this disease more widely available at less prohibitive costs. Preliminary experiments in self-administered home care suggest the feasibility of antihemophilic factors being used, as is insulin for diabetes, to prevent the manifestations of hemophilia. Recent research suggests that it may be feasible to identify the carrier state of hemophilia A in the prospective mother. However, 20 to 30 percent of hemophilia may be the result of spontaneous genetic mutations so that genetic counseling can only reduce but probably not eliminate the disease.

During manufacture of preparations containing clotting Factors II, VII, IX, and X, for patients lacking these factors, or who have severe liver disease, it was found that in some preparations several factors, including Factor X, were present in their activated form. Hemophiliacs given activated Factor X may bypass the need for Factor VIII in the clotting process. Hence, such activated human factors may become an effective treatment in those hemophilia A patients where management with Factor VIII is not possible because the blood contains concentrations of Factor VIII inhibitors too high to be overcome by administering this factor.

An advisory group recently assembled by the National Heart and Lung Institute reviewed the problem of the hemophilic patient with an acquired inhibitor to Factor VIII. Such patients exert a particularly severe demand for therapeutic Factor VIII concentrates. The natural course of such inhibitors and their relationship to the clinical status of the patients is not clearly understood. A clinical study of this problem, which would permit rational evaluation of therapeutic measures, is being planned.

Future Challenges. Currently only poorly characterized preparations of activated human factors are available which are difficult to control in the therapeutic situation. Thus, a state of excess bleeding may be changed into an equally serious state of excess clotting or thrombosis. Lastly, the exact mode of action of these factors is not known.

Additional progress in the medical management of hemophilia can be expected if home therapy, that is self-administration of antihemophilic factors, is shown to be feasible and economical. This would provide dramatic physical freedom for the patient, who at present cannot leave the environs of a treatment center, and may help prevent serious side effects such as the crippling of joints and restriction of movement. If sufficient antihemophilic factors could be produced readily, they may eventually be self-administered

prophylactically by the patient to prevent the bleeding episodes altogether. Achievement of this objective poses an important challenge.

Epidemiologic data on hemophilia such as geographic distribution, severity of the disease, accurate genetic mutation rates, morbidity, life expectancy, and mortality are currently poor or unavailable. Some patients develop antibodies to antihemophilic factors spontaneously or in response to antihemophilic factor infusions, and although work with animal factors (from calves and pigs) and activated human clotting factors is of great interest, there is currently no dependable effective way to manage such patients.

The basic information on hemophilic diseases is incomplete. A better understanding of the structure and mode of action of the clotting factors could lead to better therapeutic modalities. New, more effective preparations for treatment and improved, more efficient and cheaper methods of preparing the necessary plasma factors are needed. A common complication of blood transfusion therapy is the transmission of hepatitis virus. Recent new leads that promise to yield hepatitis-free blood components should be investigated. Thromboembolism during replacement therapy in hemophilia B (Factor IX deficiency) is now a recognized problem which needs further investigation.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue to support fundamental research on the hemophilias and related hemorrhagic disorders
- Continue support for research and development to improve the efficiency and economy of producing antihemophilic factors from human blood, animal blood, and synthetic sources
- Support clinical investigations to develop techniques for inhibiting the clot dissolving system as a potential method for decreasing bleeding crises in hemophilia
- Study the problems involved in the quality and supply of Factor IX needed for the care of hemophilia B.

Schedule. Investigator-initiated fundamental research and workshops on the development, supply, and use of antihemophilic factors for treatment will continue through FY 78.

Thromboembolic Disorders

PROGRAM GOALS

Thrombosis and embolism contribute to the high morbidity and mortality associated with diseases of the heart and blood vessels. They are implicated in several of the major causes of death in the United States. Venous thrombosis can result in pulmonary embolism and thrombosis may play a role in the clinical course of many disorders affecting virtually every organ in the body.

- A major goal is to increase understanding of the fundamental mechanisms of thrombosis.
- A second goal is to facilitate detection and treatment of thromboembolic disorders.

PROGRAM STATUS

Recent Progress. A number of clinical situations with a high risk for thrombosis and embolism have been identified. Patients with hip fractures, or undergoing hip surgery, have a very high risk of venous thrombosis and possible subsequent pulmonary embolism. Immobilized patients, particularly the elderly, are at high risk. Development of venous thrombosis is a frequent complication of heart failure and is often the first evidence of cancer. Thrombosis is also a leading complication of the use of artificial devices or oxygenators. Recent advances offer hope for increasing the acuity and sensitivity of diagnostic methods. One promising technique involves the labeling of fibrinogen with a radioisotope and measuring the amount of fibrin that becomes localized within a thrombus. This information can be used clinically to initiate therapy.

The role of clot dissolving agents, such as urokinase and streptokinase in the treatment of pulmonary embolism, has been defined by a careful clinical study. These agents may be beneficial for patients with massive pulmonary embolism, particularly those who have low blood pressure. They provide an alternative to surgical treatment. The use of these agents for other thrombolytic purposes (e.g., dissolving clots in other parts of the body) has not yet been defined.

There is promise that drugs such as aspirin, dipyridamole, and sulfinpyrazone, which inhibit the aggregation of platelets in the blood vessels, may have an important role in the prevention of a wide range of thrombotic disorders including venous thrombosis (thrombophlebitis and pulmonary embolism) and arterial thrombosis (heart attacks and stroke).

A human protein inhibitor (antithrombin) of activated coagulation factors has been extensively studied. Deficiencies of this substance may correlate with thrombotic tendencies. These studies may lead to potential therapeutic intervention. Quantitative

studies of the mechanism of platelet and fibrin thromboembolism, and of the hemostatic reactions in the living blood vessels of the microvascular system are being performed. Promising assays based on labeled fibrinogen conversion and metabolism, combined with scanning and tagging techniques, are providing tools for the detection and quantification of intravascular coagulation as well as for the localization and extent of thrombosis.

Future Challenges. The opportunities made available by progress to date should be exploited to improve prevention, detection, and treatment of venous thrombosis. Specifically, additional studies are needed and are likely to be profitable in the following areas:

- Exploration of the interaction of coagulation factors utilizing highly purified materials
- Clinical studies employing sensitive methods for the detection of clotting
- Evaluation of antithrombin as a factor in thrombotic disease.

By far the greatest public health effect of the recent advances would be the ability to prevent thrombotic diseases. Recent progress brings us closer to this goal by emphasizing risk factors, by allowing early detection and quantification of the process, and by intervention with drugs such as heparin, aspirin, urokinase, or streptokinase. However, further study is needed on these interventions. Clinical demonstration of the most effective and appropriate regimens for specific clinical situations are required.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue support of fundamental research in thrombosis and its relation to a number of disease states and epidemiologic factors, such as diet and the postoperative state
- Continue the support of clinical trials of heparin and platelet inhibiting drugs in the prevention of thrombosis in high risk patients and clinical studies in the use of clot dissolving drugs for the treatment of some thromboembolic disorders
- Support the development of methods designed to detect patients especially susceptible to thrombosis--the "hypercoagulable state"

- Continue to support the development and demonstration of techniques and instrumentation for improved detection of thromboembolic disorders

- Encourage further study of the role of animal models in thrombosis research and their value in elucidating the underlying basic mechanisms of these disorders.

Schedule. Fundamental research in thrombosis, and its relationship to various disease states and epidemiologic factors, will continue. Currently supported clinical trials in the prevention and treatment of thrombosis will continue through FY 78.

2. BIOMATERIALS

PROGRAM GOALS

The Biomaterials Program supports basic and applied research to explore the interactions between blood and natural and synthetic materials in order to develop blood compatible materials for specific uses. The development and testing of several classes of artificial materials indicate promising biocompatibility and suitable physical properties of these materials for devices and artificial organs that can provide circulatory and respiratory support.

- A major program goal is to understand the reactions, in the biological environment, of synthetic materials and chemically modified naturally occurring macromolecules.

- A second goal is to understand better the interactions between surfaces and blood components.

- A third goal is to assure the development of blood compatible materials needed for implantable diagnostic and circulatory assist devices, oxygenators, and artificial organs.

PROGRAM STATUS

Recent Progress. Improved biomaterials suitable for several uses have been produced by surface grafting and bonding processes. The possibility of developing blood compatible living cell surfaces by tissue culture techniques presents an alternative to completely synthetic materials. Increased efforts are being made in basic research to assess the changes in blood components that result from their contact with natural and synthetic surfaces. Conversely, the changes in the biomaterials produced by contact with blood are also being studied.

Several polymers based on segmented polyetherurethanes combine good physical performance with reasonably good blood compatibility. These polymers are useful in circulatory assist devices, and as substrates for blood compatible surface coatings.

A new class of so-called "springy" polypropylene materials appears to offer a unique combination of physical properties for potential prosthetic applications. These materials can imitate many of the mechanical features of living tissues. Blood compatibility may be imparted to them by one of several surface treatment techniques currently undergoing further development.

New techniques to impart blood compatibility to otherwise noncompatible polymers are continually being developed. Surface grafting of hydrogel systems, involving covalent bonding by a new vapor-phase technique, shows considerable promise. Heparinized materials that show excellent thrombo-resistance for up to six hours are being clinically evaluated for use in a number of medical devices such as catheters and shunts. Ion-plated and vacuum-vapor deposited carbons on polymeric and nonpolymeric surfaces are being tested for their compatibility with and erosion resistance to blood.

Other candidate materials, including polyalkylsulfones and fluorinated ethyl cellulose, are being studied for use in membrane oxygenators. The materials show blood compatibility and their gas-to-blood transfer rates for oxygen and carbon dioxide may be superior to currently used polymer films. Further evaluation of these materials is proceeding.

Continued improvement in testing methods for blood compatibility of biomaterials has resulted in more rapid and effective biological evaluation of candidate biomaterials. These improved systems now provide a national resource for such testing and evaluation.

To elucidate the general parameters that determine the blood compatibility of surfaces and of the natural components of the cardiovascular system, studies are being conducted to determine how natural and modified naturally occurring macromolecules, such as collagen, elastin, and mucopolysaccharides, interact with blood.

Future Challenges. In order to develop the basic information for the synthesis of new materials for specific biomedical applications, further investigation of the fundamental aspects of interactions between blood and biomaterials, as well as the mechanical and physicochemical properties of natural tissues, must be pursued. The possibility of using natural tissues as models to guide in the design and development of synthetic systems with properties approximating those of the natural tissues offers a tremendous future challenge. Changes which occur both in the blood proteins and in the surface-absorbed protein need further investigation and better understanding.

Additional development of blood compatibility testing and related facilities are needed to improve currently used methodologies, reduce the expense of animal work, and explore further the effects on the various blood elements of both natural and synthetic biomaterials.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue support of basic and applied research aimed at better understanding of the interactions of blood components with both synthetic materials and natural biopolymers
- Explore further the synthesis and preparation of biocompatible materials suitable for specific medical applications
- Develop improved methods of physicochemical and biological characterization and evaluation of candidate materials for biomedical applications
- Initiate, when applicable, clinical trials of promising, well characterized, and animal tested biomaterials.

Schedule. Both basic and applied research on the interactions of blood components with synthetic and natural materials will continue as will the development of biocompatible materials for specific use in medical therapy. Clinical trials of promising, well characterized candidate materials may begin in FY 76.

3. SICKLE CELL DISEASE AND OTHER DISORDERS OF THE RED BLOOD CELL

The three groups of disorders considered in this section include sickle cell anemia (disease) and sickle cell trait, conditions closely related to sickle cell disease such as Cooley's anemia, and defects affecting the red blood cell membrane and enzyme systems.

Sickle Cell Anemia and Sickle Cell Trait

PROGRAM GOALS

Sickle cell trait is a relatively benign "carrier state," characterized by the presence of both normal hemoglobin (Hb A) which is inherited from one parent and sickle cell hemoglobin (Hb S) which is inherited from the other parent. Under normal conditions persons with sickle cell trait rarely have clinical disease. However, approximately 1 in every 500 black babies is born with genes for sickle hemoglobin inherited from both parents, and therefore has sickle cell anemia.

Despite knowledge of the precise hereditary defect in the sickle hemoglobin molecule, there is as yet no specific therapy for sickle cell anemia and complications of the disease must be treated as they arise. Therefore, a balanced program must address a variety

of problems, from increased understanding of the red cell to treatment of the patient and education of the community in which he lives. (See section on Prevention, Control, and Education Programs).

- The primary research goals are to increase fundamental understanding of sickle hemoglobin, the sickling process, rheology (blood flow), and complications of this disorder; and to develop improved therapy for the sickle cell crises.

PROGRAM STATUS

Recent Progress. Fundamental research in sickle cell disease continues to advance our understanding of this disorder. Red cells containing sickle hemoglobin may undergo distortion in shape when subjected to low oxygen tensions. The rigid forms that result may cause blockage of the microcirculation and lead to the painful episodes or crises.

The National Heart and Lung Institute continues to coordinate the Health, Education, and Welfare's Sickle Cell Disease Program initiated by the President in 1971. The major objectives of this program are: (1) to foster research and development both at the fundamental and clinical levels; (2) to initiate and expand community education, screening, and counseling programs; (3) to educate medical and allied health professionals concerning the problems of sickle cell disease; (4) to improve clinical care for victims of sickle cell disease. The last three objectives are discussed in the section on Prevention, Control, and Education Programs.

The first National Sickle Cell Symposium was held in June 1974 to assess the current status of sickle cell disease research, and to develop plans for new scientific approaches in the coming year. Proceedings of this meeting are being published and the Report of the Analysis and Evaluation Committee of this symposium is now available.

The investigation of agents which may alter the sickling process continues. It includes the investigation of such compounds as sodium cyanate, carbamyl phosphate, alkylating agents, zinc and other trace metals, and various amino acids. Preliminary studies are being undertaken to examine the feasibility of treating patients by extracorporeal means. The patient's red cells are removed and incubated with the agent under trial and then placed back into the circulatory system. This approach allows maximal contact of the agent with the red cells containing sickle hemoglobin and minimizes the possibilities of side effects through contact between the agent and other body proteins. Clinical trials have shown that urea is not effective in the treatment of patients in crisis.

Higher animals, including man, have the genetic capability of producing more than one type of hemoglobin. Also, the type of hemoglobin produced can vary with the physiological state. For example,

in humans, production of fetal hemoglobin (Hb F) converts to production of adult hemoglobin (Hb A) shortly after birth and in some animals (sheep, goats) a reversion from adult to fetal hemoglobin production can be produced by anemia. Tissue culture systems have been developed to study the mechanism of this genetic switch, which is under the control of the hormone, erythropoietin. Learning how to switch from adult to fetal hemoglobin production would be expected to be of benefit to patients with sickle cell disease.

Future Challenges. Basic epidemiologic data on the prevalence and distribution of these diseases, particularly the prevalence of carrier states, are required.

Knowledge of the biology of the red cell, the mechanisms of intravascular sickling, the effects of combinations of sickle hemoglobin and other abnormal hemoglobins, and of the effect on the red cell of agents that may prevent or reverse sickling are incomplete. Further research is needed to gain the information necessary for rational therapy.

The search for therapy that is effective, safe, and simple must continue. As promising therapies are developed, they must be tested in clinical trials. Simple, rapid, accurate, and reliable screening techniques need to be developed to detect hemoglobin variants, including sickle hemoglobin.

In developing interfaces with other agencies and organizations, the greatest challenge for the future is to develop a well-coordinated and uniform approach throughout Federal departments and agencies on research related to abnormal hemoglobins.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue the support of basic and clinical research through investigator-initiated research grants and comprehensive Sickle Cell Research Centers
- Continue clinical studies to explore the use of antisickling agents and other therapeutic approaches to painful crises
- Consider the recommendations of the First National Sickle Cell Disease Symposium in exploring promising research opportunities
- Develop and implement evaluation methods to assess the overall progress of the program and its future directions
- Continue to develop interfaces with other Institutes of the National Institutes of Health and other Federal

agencies including the National Institute of Arthritis, Metabolism, and Digestive Diseases; the Center for Disease Control; the Health Services Administration; the Department of Defense; the Department of Labor; and the Veterans Administration.

Schedule. Fundamental research in sickle cell anemia and sickle cell trait will continue. Clinical studies of promising leads will be carried out as these develop.

Cooley's Anemia and Related Hemoglobin Variants

PROGRAM GOALS

Cooley's anemia (thalassemia) is an inherited disorder of hemoglobin synthesis resulting in anemia and a shortened life expectancy. Adequate treatment for the disease is unavailable. Blood transfusions to treat the anemia cause a serious excess of iron to accumulate in the patient's body.

- The major goal of the program is to increase the fundamental knowledge of the control mechanisms affecting hemoglobin synthesis.
- A second goal is to develop simple, effective screening tests to identify carriers of this genetic abnormality.
- A third goal is to improve and evaluate transfusion therapy and to find a means of removing the excess iron resulting from the chronic transfusions.
- A fourth goal is to explore other possible treatment modalities.

PROGRAM STATUS

Recent Progress. It has now been demonstrated that Cooley's anemia is the result of a defect in the messenger ribonucleic acid (mRNA) step of the hemoglobin production. Messenger ribonucleic acid carries genetic information to the protein manufacturing material. A biologically active mRNA has been isolated from bone marrow and peripheral cells of patients with thalassemia.

Future Challenges. Our understanding of the molecular basis of Cooley's anemia continues to grow, but we do not yet know how to correct it. Transfusions are given to sustain life. While these give temporary relief, they burden the body with excess iron that cannot be eliminated through normal processes. A future challenge is to develop improved ways of reducing the iron overload in the body and thereby prolong the life of patients with Cooley's anemia.

Fundamental research must continue because the development of a rational basis for therapy will depend upon control of events at the molecular level. Further work is needed to develop simple, accurate methods for identifying carriers with Cooley's trait. Standardized methods and establishment of a reference "bank" of controls for such testing are still needed. The development of better modes of diagnosis, effective and safe iron-chelating agents (for the removal of excess iron), and other treatments for the management of Cooley's anemia are required. The ultimate challenge remains to find methods to correct the molecular genetic process leading to this defect.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue to support basic and clinical research in Cooley's anemia and to develop effective screening, counseling, and treatment techniques
- Carry out clinical trials to test the efficacy of chelating agents to prevent and/or manage the iron overload due to transfusion therapy
- Continue to coordinate efforts with other Institutes of the NIH and other Federal agencies in support of basic and clinical studies in Cooley's anemia to develop improved methods of detecting the carrier state and better neonatal diagnosis.

Schedule. Programs in research on Cooley's anemia and related red blood cell disorders will continue. It is anticipated that targeted clinical research efforts may be initiated in FY 75 or FY 76. Intramural programs relating to Cooley's anemia will continue.

Red Blood Cell Membrane and Enzyme Systems

PROGRAM GOALS

Disorders of the red cell membrane and its intracellular enzyme systems are responsible for a small but significant number of clinically important cases of anemia. Perhaps more importantly, because blood is simply and readily withdrawn for study, the red cell provides a convenient model for studying membrane physiology and the metabolic pathways common to cells in many organs of the body. Red blood cells preserved outside the body (as in blood or red cell concentrates prepared for transfusion) require intact metabolism and intact membrane function for survival after transfusion. Therefore, a better understanding of these systems is applicable not only to red cell preservation but also to the

preservation of other body cells, tissues, and organs to be used in human transplantation.

- The major research goal is to increase the understanding of membrane structure and function, and intracellular metabolic activities.

- A second goal is to apply this information to clinical medicine.

PROGRAM STATUS

Recent Progress. Progress continues in our understanding of the red cell, its membrane, its enzyme systems, and the properties which contribute to the cell's viability and proper physiologic function in the circulation. Studies continue on such physical properties as deformability, adhesiveness, viscosity, and the physicochemical factors involved in the interaction of blood cells with one another and with plasma. Biochemical, clinical, hematologic, and genetic investigations of diseases caused by inborn errors in the metabolism of red cells continue to provide further insight into these problems. Basic studies of the transport of materials across cell membranes continue to capitalize on the red blood cell as a convenient preparation for the study of relationships between chemical properties and the functions of cells in general and the red cell in particular.

Future Challenges. Further study is still required to understand the mechanism underlying anemia resulting from red cell enzyme deficiencies. In order to extend the preservation of red cells for transfusion beyond a brief period of a few weeks, factors regulating their metabolism must be better understood. The establishment of reference laboratories for diagnosing and investigating red cell membrane and enzyme disorders, and specifically for diagnosing rare red cell deficiencies, remains a challenge. The increased susceptibility to lysis by certain drugs or during illness of red cells deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD) requires further study.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue the support of basic research on the normal red cell membrane and enzymes as well as on red cell enzyme and membrane disorders

- Seek to identify and establish reference laboratories for the diagnosis and investigation of red cell enzyme and membrane abnormalities

- Carry out comprehensive targeted evaluation studies of the status of these problems, opportunities for research, and the identification of specific short- and long-range goals for meeting these challenges.

Schedule. Support for basic investigator-initiated research will continue. Efforts during FY 75 and FY 76 will emphasize evaluation of the status of problems and the identification of short- and long-range goals.

4. BLOOD RESOURCES

Blood is a valuable but limited natural resource, the ever expanding need for which demands its safe and efficient utilization. The use of this life-giving substance constitutes an important therapy essential to the nation's health. Transfusions save thousands of lives annually, not only of the injured, but also of people undergoing surgery or suffering from various diseases affecting blood or its components. Blood can now be stored for emergencies. About nine million pints of blood per year are collected in the United States for transfusion purposes. Maintenance and proper use of this national supply of blood and blood components are critical and require care and vigilance. The demand for blood is increasing as new therapeutic uses are found; however, the supply of blood from donors is limited. Hence, economical, efficient use must be made of the available blood resources, wastage of blood must be eliminated, a clearer agreement must be reached within the medical profession regarding the indications for therapeutic use of whole blood and blood fractions, and volunteer blood donation must be stimulated.

The 1972 National Heart, Blood Vessel, Lung, and Blood Act significantly expanded the authority and responsibility of the Institute in areas which include the use of blood, blood products, and the management of our nation's blood resources. The research being implemented relevant to blood resources will be discussed in four subprograms: The Nationwide Blood System, Safety of Blood Therapy, Blood Component Therapy and Blood Substitutes, and Transplantation Biology.

Nationwide Blood System

PROGRAM GOALS

The U.S. blood resource complex, while providing essential services and products, at present does not consistently maintain adequate supplies, nor the highest attainable quality of blood therapy. The National Heart and Lung Institute played a key role in the development of the national blood policy and will be active in its implementation. It fosters collaboration, coordinates programs, and provides research and development support for joint programs with the Office of the Secretary of the Department of Health, Education, and Welfare; the Bureau of Biologics of the Food and Drug Administration; and the private sector of the blood banking community.

- The primary goal of the program is to promote and maintain an adequate blood supply of the highest attainable quality.

PROGRAM STATUS

Recent Progress. The Secretary of the Department of Health, Education, and Welfare has approved the establishment of an American Blood Commission through which the private sector in blood banking will develop and submit plans for implementation of the National Blood Policy. The Institute will consider these plans in determining future research priorities aimed at fostering the nationwide blood program.

Several studies were recently completed and published on the development of a nationwide blood system. These include:

- Cost-finding methodologies adaptable to the blood banking community which can form a basis for establishing uniform, rational pricing policies.

- Analysis and design for a National Blood Resource Information System based on standardized reporting applicable to the blood banking community of this country. Implementation of an information system based on this study will be carried out through the Bureau of Biologics of the Food and Drug Administration in collaboration with the National Heart and Lung Institute.

- A report on the feasibility of conducting a study to determine the incidence of post-transfusion hepatitis.

- A pilot study of the epidemiology of post-transfusion hepatitis.

- A report on regionalization in present blood supply systems which will be made available to the American Blood Commission and the Secretary's Office as a resource document.

The Institute also participates in the US-USSR Cooperative Program in Blood Transfusion. This program places particular emphasis on hepatitis and the use of blood components and blood substitutes with particular reference to patients undergoing cardiovascular surgery.

Future Challenges. The present nationwide blood system and blood service complex have enormous strengths and in the main they have served the American people well. However, they remain fragmented and poorly coordinated, thereby resulting in inefficient use of

this vital resource. This inefficiency sometimes compromises the quality of blood provided to the patient. The challenge is the optimal utilization of blood. This must be addressed through the combined efforts of the National Heart and Lung Institute, other government agencies, and private organizations within the blood banking community. Some specific challenges are:

- The implementation of cost-effective systems and of information control systems
- The improvement of approaches to determine appropriate utilization of blood and blood products
- The assessment of the immediate and future impacts of their utilization on the national blood resource.

PROGRAM PLANS

Actions. The Institute plans to:

- Coordinate its efforts with private and public organizations involved in blood banking toward the creation of an all voluntary blood donation system and regional integration of this system to increase its effectiveness
- Continue to expand its catalytic role in implementing the National Blood Policy by working with the American Blood Commission and other Federal agencies
- Continue to support the development of technology to improve the utilization of the nation's blood supplies, including techniques which will facilitate economic introduction of frozen blood into the National Blood System.

Schedule. Studies of the nationwide blood system, blood collection, distribution, and utilization will continue in support of the national blood policy to be implemented by the American Blood Commission. Continued collaboration with other agencies for the development of uniform data systems is planned.

Safety of Blood Therapy

PROGRAM GOALS

Blood transfusions play an important role in saving lives. Unless great care is taken in the collection, preparation, and storage of the blood intended for transfusion, it may also transfer disease. The risk of infection or toxic reaction due to transfusion of blood and blood products remains at an unacceptably high level. Improved carrier detection and better removal or inactivation of hepatitis virus and other infective agents from blood and blood products

are needed. Effective immunization methods also need to be developed, as does an improved technology for the development and application of a standardized method to determine toxic components in blood and blood products.

- A major goal of this program is to eliminate post-transfusion hepatitis and other infections.
- A second goal is to identify and remove toxic components leached from containers and other materials used during transfusion of blood.
- A third goal is to reduce contamination during the handling of blood.
- A fourth goal is to eliminate human errors in matching donor blood with that of the patient by use of improved identification systems.

PROGRAM STATUS

Recent Progress. Through the cooperative efforts of the National Heart and Lung Institute and several other agencies, comprehensive prospective epidemiologic studies of post-transfusion hepatitis are being carried out. Clinical studies have indicated that hepatitis B immune globulin is not effective in the clinical treatment of acute fulminant hepatitis. New tests have been developed for identification of the hepatitis A virus. Preliminary results suggest that most post-transfusion hepatitis which is not of the B type is also not of the A type. Therefore, additional causes of hepatitis continue to be of concern in blood therapy. Standardized panels of hepatitis B antibody (a set of vials containing antigens or antibodies of specified subtype and known potency) have been made available to qualified investigators to accelerate their studies of hepatitis. The risk of transmission of hepatitis in various blood fractions, such as prothrombin complex (coagulation Factors II, VII, IX, and X) may soon be eliminated by new techniques which inactivate the hepatitis B virus.

The chimpanzee is the only known animal model which develops clinical hepatitis B. Importation of these animals is limited and expensive. Furthermore, as indicated by serologic tests, most imported animals have already been exposed to hepatitis B. As few chimpanzee breeding facilities exist in the United States, additional facilities have been established to provide serologically negative animals to qualified investigators in hepatitis research.

Standardized methods to determine amounts of plasticizer leached from plastic containers used in blood transfusion now allow study of the clinical importance and possible toxicity of these materials in blood therapy. Work is nearing completion on methods to insure sterility during processing and to extend the period of safe use of thawed, frozen red blood cells.

Future Challenges. Reduction of the risk of post-transfusion hepatitis remains a major challenge. While recent advances have been made in the understanding of this hepatitis and its transmission, methods to prevent the risk of infection due to transfusion must be improved further and must be implemented in the national practice of blood transfusion and blood banking. This will require the development and application of new identification and screening techniques to detect and remove hepatitis virus from blood to be used for transfusion. This should include detection of chronic virus carriers among blood donors and methods to eliminate the carrier state. Infections in transfused patients must be studied further and means to prevent them developed and implemented.

The safest form of transfusion therapy is the retransfusion (autologous transfusion or autotransfusion) of the patient with his or her own blood previously collected and stored to be kept on hand for potential future emergencies. Further research into the feasibility of autotransfusion, both through the banking of the patient's own blood prior to anticipated needs and/or the collection and recycling of the patient's blood during major surgery, is necessary. Proper application of autotransfusion may also reduce the individual's demands on the nation's blood resources.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue support of basic and applied research in hepatitis and other infectious or toxic reactions due to transfusion
- Continue the prospective study of post-transfusion hepatitis to define the threat of hepatitis and implicate infectious donor units, to identify, if possible, the etiology of non-A, non-B hepatitis, and to study the epidemiology of the long-term risk of chronic hepatitis from transfusion
- Develop more sensitive, specific tests to detect hepatitis in blood units
- Explore the feasibility of international collaboration in the reduction of hepatitis in blood through the US-USSR Cooperative Health Exchange as well as other mechanisms
- Maintain research resources, including animals and specific reagents, for hepatitis research
- Seek to further extend the period of safe use of thawed, frozen blood

- Seek to reduce the complications from massive transfusions by various means.

Schedule. Basic and applied research on infectious and toxic reactions to transfusion are expected to continue. Support for research resources for use in hepatitis research should peak in FY 77 and taper off as these resources become self-supporting. Studies on other aspects of the safety of blood and blood products will continue through FY 80.

Blood Component Therapy and Blood Substitutes

PROGRAM GOALS

The medical demand for red blood cells sets the pace for the collection of whole blood. Patients who need red cells usually do not need the other blood components. Currently, whole blood is used in more than three out of four transfusions, although strong evidence indicates that it is required in less than one out of four cases. Reducing the use of whole blood not only constitutes good medical practice, but also increases the availability of blood components, often in short supply.

- A major goal is to improve methods both for blood cell separation and preservation and for plasma fractionation, so that the many important components can be recovered fully and economically.

- Another goal is to develop clearer indications for the use of blood components and better methods to assess their effectiveness.

PROGRAM STATUS

Recent Progress. New methods of plasma fractionation continue to be evaluated to find more efficient and economical methods of producing blood derivatives. Recently a search was initiated for new potentially useful products from plasma fractionation. Clinical feasibility testing of the potentially useful fractions are being carried out to determine which of the many proposed plasma fractions merit large-scale production and clinical use. Methods which will permit preservation of platelets for extended periods have been developed and are under clinical investigation. Studies are underway to demonstrate the feasibility of leukocyte preservation. Preparations of immune serum globulin for intravenous administration to selected patients are being clinically evaluated.

Future Challenges. Further work is needed on separating, storing, and maintaining the viability and function of cellular components and other fractions of blood for use in component therapy.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue to support the development of new methods for blood component and derivative production and the search for additional useful plasma fractions
- Complete the testing of platelet preservation methods
- Explore the current status of and indications for component therapy and define additional research needs
- Explore the current status of leukocyte transfusion therapy and outline needs and opportunities for further research
- Continue the US-USSR Cooperative Program in blood transfusion
- Encourage and support research to develop, test, and promote the utilization of blood substitutes both for plasma volume expansion and for oxygen delivery.

Schedule. Support for the development of new blood products and methods for preparation of blood components and derivatives will continue. Educational activities to encourage utilization, whenever possible, of blood components rather than whole blood will increase. (See section on Prevention, Control, and Education Programs.) Activities related to the implementation of US-USSR cooperative programs, should increase during FY 76. Research and development to promote the utilization of blood substitutes is expected to increase.

Transplantation Biology

PROGRAM GOALS

The transplantation biology subprogram of the Institute encourages and supports fundamental research in immunology, immunogenetics, and other aspects of transplantation biology so as to develop methods suitable for tissue and organ banking. In addition, the program seeks to study the feasibility of using the established and evolving blood banking system to foster tissue and organ banking networks and to implement an effective nationwide transplantation system.

- A major goal is to prevent transplant rejection due to sensitization of the recipient to histocompatibility antigens during transfusion.
- Another immediate goal is to continue clinical studies to improve platelet and white blood cell transfusion therapy.

- A third goal is to determine the feasibility of regional blood centers performing tissue typing and storage functions.

- A fourth goal is to explore the possible role of regional blood centers in collecting, processing, and distributing tissues and organs for transplantation.

PROGRAM STATUS

Recent Progress. The sensitization to histocompatibility antigens of prospective transplant patients by transfusion of white blood cells can be significantly reduced by removing the leukocytes from the transfused blood. Methods being investigated include freezing and thawing, filtration and double centrifugation of the blood. The clinical significance of these findings remains to be determined.

Future Challenges. Further development of organ preservation techniques, and devices for storing isolated organs must be developed before a system of regional or national organ procurement is feasible. Such development, and its implementation, will require additional fundamental research in organ preservation.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue the support of fundamental research in immunology, immunogenetics, and other aspects of transplantation biology

- Explore the feasibility and appropriateness of using the evolving regional blood system to provide a national system for tissue and organ procurement, preservation, typing, and distribution.

Schedule. Support for basic research relating to transplantation biology technology will continue. Studies of the feasibility of a regionalized national system of tissue and organ procurement, preservation, typing, and distribution, are expected to increase during FY 75 and FY 76.

PREVENTION, CONTROL, AND EDUCATION PROGRAMS

For most diseases, prevention, rather than treatment, holds the greatest promise of materially reducing disability, death, and complications. The Act increases the responsibility of the Institute to initiate and carry out prevention, control, and education activities to assure the application of the knowledge and technology developed through its research program in Blood Diseases and Blood Resources. The Institute attempts to integrate the prevention, control, and education activities with the research and development activity of each program area. Major prevention, control, and education programs are addressed to hemophilia, thromboembolic disorders, sickle cell anemia, Cooley's anemia, and the development of effective blood resources.

1. HEMOPHILIA

PROGRAM GOALS

Public awareness is fundamental to the management and prevention of hemophilia. Treatment is very costly and must be continued throughout the patient's lifetime and thus demands a large fraction of the nation's blood resources. Since the disease is hereditary, education of the public can be instrumental in its prevention.

- The goal of this prevention program is to educate the patient, the physician, and the general public so that patients with hemophilia and their families may make informed decisions regarding their own lives.

- Another goal is to improve the quality of life for the hemophiliac and his family through programs of screening and genetic counseling.

PROGRAM STATUS

Recent Progress. A recent workshop on Factor IX (the factor lacking in hemophilia B) was sponsored jointly by the National Heart and Lung Institute, the Food and Drug Administration, clinicians, and manufacturers. Recommendations were discussed aimed at reducing the thrombogenicity, improving the safety, and increasing the quality control of Factor IX therapeutic products to be used for the treatment of hemophilia B.

Workshop and laboratory studies have been undertaken to determine the adequacy of current and potential tests to detect the carrier state for hemophilia in females. A double-blind study is being conducted by investigators from across the world to evaluate critically the efficacy of the technique now being used to detect hemophilia A carriers.

The Institute's national survey of hemophilia treatment provides information from which effective plans can be developed for the study and treatment of this disease. In an effort to improve current treatment, evaluation of a comprehensive health care delivery model and of home care are underway.

Future Challenges. Plans are being developed to conduct demonstration projects to stimulate the establishment of comprehensive centers where needed and to integrate such centers into overall regional care systems for hemophilia. The long-range goals of these centers over a five-year period would be as follows:

- Evaluate and, where applicable, standardize treatment, facilities, and products
- Conduct epidemiological studies of patient distribution and conditions
- Determine effective management of patients having Factor VIII inhibitors
- Conduct relevant education/information programs to insure informed participation by patients, public, and health care professionals
- Strengthen patient organizations, primarily through the National Hemophilia Foundation, to provide personal and group support from the patient's point of view
- Provide blood products in adequate amounts and of highest obtainable quality
- Develop comprehensive diagnostic/care centers evenly distributed across the United States and sufficient in number to cover 50 percent of the patient population.

PROGRAM PLANS

Actions. The Institute plans to:

- Explore, in cooperation with other agencies, information, education, and genetic counseling techniques aimed at improving hemophilia therapy and preventing hemophilia
- Study and evaluate methods to develop a comprehensive care potential for hemophilia in areas where limited facilities exist
- Evaluate the existing health care facilities in hemophilia and develop a data base upon which standards of health care for hemophiliacs can be developed and an integrated national network of health care can be planned.

Schedule. Studies of hemophilia care systems during FY 75 and FY 76 will be coupled with education and demonstration activities, increasing through FY 78 to develop recommendations concerning the implementation of regional comprehensive care systems.

2. THROMBOEMBOLIC DISORDERS

PROGRAM GOALS

Thromboembolic disorders contribute to, or cause, a variety of diseases. The prevention and control of these disorders depend on the identification of persons at high risk, early diagnosis of progressing thrombosis, and effective treatment to retard the development or minimize the extent of thrombosis and embolism.

- The primary goal of prevention, education, and control programs in thromboembolic disease is the reduction of disability and mortality through the control of risk factors and through the wider application of improved detection and treatment regimens.

PROGRAM STATUS

Recent Progress. The Institute continues its participation in international congresses on thrombosis and hemostasis and it has supported conferences and workshops in conjunction with other organizations. These have dealt with the chemical and biological aspects of heparin and its clinical applications and the role of thrombosis in the pathogenesis of acute myocardial infarction. The results of the recently concluded pulmonary embolism trials have been published. These results describe the type of patient likely to benefit from urokinase and streptokinase therapy.

Future Challenges. Continuing efforts must be made to stimulate and facilitate rapid and wide dissemination of information on the advances in thrombosis detection, treatment, and related fields. The role of prophylactic antithrombotic therapy must be clarified.

In addition, the coordination with other agencies and the private sector in the techniques for educating the medical community and the public in general about risk factors of thrombosis, their prevention, and detection, will continue.

PROGRAM PLANS

Actions. The Institute plans to:

- Sponsor a workshop on prophylactic antithrombotic therapy
- Explore, in coordination with other agencies, techniques for educating the medical community and the general public about thromboembolic disease.

Schedule. These coordinated activities are ongoing and will increase in the next few years.

3. SICKLE CELL ANEMIA AND COOLEY'S ANEMIA

PROGRAM GOALS

Despite current research in and clinical knowledge of sickle cell disease and Cooley's anemia, the general public, including possible victims of these diseases, does not have an adequate understanding of these disorders and their significance. Both diseases cause great suffering and both diseases are transmitted by carriers to their offspring if both parents carry the trait. Education and control programs are necessary to lead to better understanding of these diseases by the public.

- The goals of the control programs are to inform the public and the medical profession about sickle cell disease and Cooley's anemia and other hemoglobinopathies and to demonstrate techniques for appropriate screening and counseling.

PROGRAM STATUS

Recent Progress. Programs have been developed to expand the dissemination of information about these diseases and to provide continuing education for physicians and related health personnel. The programs emphasize both established approaches and new developments in the understanding of sickle cell disease, Cooley's anemia, and other hemoglobin disorders. Where available and appropriate, standardized techniques for screening, counseling, and diagnosis are being used. Continuing education programs have been sponsored by several sickle cell centers and clinics. The initiation of a sickle cell education program, to be carried out by nongovernmental groups, will result in a marked increase in public awareness about, and better knowledge of, the sickle cell state. An evaluation has been initiated of the control activities in the Screening and Education Clinics administered by the Health Services Administration, Sickle Cell Office.

Pilot studies have been supported for a program of education, screening, and counseling for individuals with thalassemia states (Cooley's anemia).

Future Challenges. Accurate, up-to-date information on these diseases must be provided to the public by expanding appropriate community education, screening, and counseling programs. Programs must be provided to educate medical and allied health professions to deal with the problems of these diseases and their resolution. Counseling and guidance techniques must be developed to assist individuals in managing the psychological, social, and economic problems resulting from these disorders so that they may attain their maximum potential in life.

Projects in screening and diagnostic testing of hemoglobin abnormalities are presently in an early phase. Future challenges in

this area include the development of accurate neonatal diagnosis of abnormal hemoglobins and of innovative methods of education and genetic counseling. The greatest immediate need is for dissemination of accurate information to the public regarding the meaning of sickle cell trait and sickle cell anemia.

PROGRAM PLANS

Actions. The Institute plans to:

- Continue collaboration with other Federal agencies to develop programs which provide accurate dissemination of information to the general public and the population groups at risk; to educate and assist health professionals, allied health professionals, educators, employers, and insurers concerning these disorders; and to provide effective counseling to affected individuals, including proper rehabilitation, when applicable

- Evaluate clinical approaches to the treatment of these disorders and seek to assure that effective approaches are incorporated into the health delivery system

- Support a comprehensive education program to provide public and health professionals with up-to-date, accurate information on sickle cell anemia and trait, Cooley's anemia, and other hemoglobin disorders, and publicize the availability of screening, counseling, and referral services

- Study screening and counseling techniques used for Cooley's anemia to develop recommendations for their application on a broader scope.

Schedule. Support for the development of sickle cell education programs should increase. By FY 77, the studies of screening and counseling techniques should result in recommendations for application on a broad scale.

4. BLOOD RESOURCES

PROGRAM GOALS

The appropriate treatment, prevention, and control of many major diseases relies heavily on adequate therapy with blood components and derivatives. An adequate supply of the highest quality must be provided for effective treatment and to avoid the transmission of disease. The Institute's Blood Resources Program seeks to foster the use of improved methods for the collection and distribution of blood components and derivatives. A program to educate

the professional and lay public on the optimal use of blood resources and the effective management of the blood banking system will continue.

- The overall goal of the prevention, education, and control programs is to achieve more effective overall management of the nation's blood resources.

PROGRAM STATUS

Recent Progress. A program was recently begun to produce and pretest educational material to foster the improved use and application of blood component therapy in the medical and blood banking communities.

Programs are being developed to educate the technical and medical professions in the optimal utilization of blood and blood components. Information gained from special studies of education programs on the risks of hepatitis and means for reducing such risks is being disseminated through organized workshops and publications of the Institute.

Future Challenges. The National Heart and Lung Institute will consider the plans of the American Blood Commission in determining future priorities in prevention, control, and education programs aimed at fostering a nationwide blood program.

PROGRAM PLANS

Actions. The Institute plans to:

- Assist in implementing a National Blood Data Collection System to provide comprehensive, continuous information and evaluation concerning the nation's blood supply, its size, distribution, and use
- Participate with other agencies in a concerted attack on hepatitis
- Continue to expand the educational efforts in the blood banking and medical communities to encourage the optimal utilization of blood and blood components.

Schedule. Development, evaluation, and implementation of education programs aimed at safe use and optimal utilization of blood and blood products will continue. Cooperative studies and implementation of uniform blood resources data and information systems will continue through FY 78.

PROGRAM COORDINATION

The National Program in Blood Diseases and Blood Resources, with its long-range and broad goals, offers the Institute an opportunity to stimulate collective efforts on a number of levels in other organizations and all sectors of our society. The multiplier effect of using other national resources combined with the direct effects of the Institute's own efforts extends the effectiveness of the National Program well beyond the borders of the Institute.

In blood diseases and blood resources, the National Program addresses several key research and prevention activities such as the amelioration of the effects of sickle cell disease, Cooley's anemia, hemophilia, thromboembolic disorders, hepatitis, and the improvement of the management of the nation's blood resource so vital to the treatment of many diseases. Many of these efforts involve close coordination with other agencies. Formal coordination, through the Interagency Technical Committee, as well as informal collaboration, take place on a number of program levels. Cooperative, coordinated efforts responsive to the National Program are summarized below for each categorical disease area.

- Sickle Cell Disease. The Institute will continue to develop interfaces with other Institutes of the National Institutes of Health and other Federal agencies including the National Institute of Arthritis, Metabolism, and Digestive Diseases; the Center for Disease Control; the Health Services Administration; the Department of Defense; the Department of Labor; and the Veterans Administration.

- Cooley's Anemia. The National Heart and Lung Institute, in cooperation with other NIH components, with private organizations involved with Cooley's anemia, and with the scientific community have agreed on priorities for research in this area.

- Hemophilia. The Institute maintains a cooperative working relationship with the National Hemophilia Foundation. Collaborative activities include program planning, information exchange, and research. The Foundation had significant input into the development of the National Program, and discussions continue to assure that the programs of the Institute and the Foundation are complementary and mutually supportive of each other.

- Hepatitis. A Hepatitis Liaison Committee, composed of representatives from all government organizations funding hepatitis research, has been established to coordinate information exchange and to advise all research organizations on program needs and potentials. Comprehensive prospective epidemiologic studies of post-transfusion hepatitis are being carried out through cooperative efforts. A Hepatitis Policy Liaison Committee, consisting of representatives from the Bureau of Biologics, the National Heart and Lung Institute, and the National Institute of Allergy and Infectious Diseases, coordinates extramural hepatitis research activities funded by these agencies.

- Blood Resources. The Institute plays a key role in the continuing development of a National Blood Policy. It fosters collaboration, coordinates programs, and provides research and development support for joint programs with other NIH components; the Office of the Secretary of the Department of Health, Education, and Welfare; the Office of the Assistant Secretary of the Department of Health, Education, and Welfare; the Bureau of Biologics of the Food and Drug Administration; and the private sector of the blood banking community.

- Manpower Development. The Institute, in cooperation with other agencies and societies, carries out a continual assessment of the national manpower development needs in research and clinical hematology and in blood banking. These assessments form the basis for proposed manpower development and training activities supported by the Institute.

- International Collaboration. The US-USSR Health Exchange Program is a highly structured, collaborative international program.

  Key activities related to the National Program which are being implemented under this agreement include a program in blood resources. This program encompasses collaborative efforts in blood transfusion, blood components, and prevention of hepatitis, with particular reference to cardiovascular surgery. Exchange of information, exchange of health professionals, and periodic meetings between American and Soviet scientists are some of the ways in which this scientific cooperation is carried out. Plans have been made for coordinated investigations to be initiated during 1975 through 1976 on:

  - Approaches to the prevention of hepatitis in blood transfusion, particularly during cardiovascular surgery

  - The use of whole blood, blood components, blood derivatives, and blood plasma substitutes with particular emphasis on cardiovascular surgery.

MANPOWER RESOURCES

The development and maintenance of diverse types of highly skilled manpower are of great importance to the implementation of our national efforts in blood diseases and blood resources. In their recent reports, the National Heart and Lung Advisory Council and the Institute have placed great emphasis on the need to develop skilled manpower, both to replace the losses from the present pool, and to supply evolving needs.

Recent studies of staff positions in hematology and a survey of blood bank physicians estimated that approximately 20 percent of the funded positions in blood banking research are unfilled. Because of the rapidly increasing scope of activities in blood banking and the importance to the nation's health of an adequate supply of donor blood, well-defined training programs must be established to fill these manpower needs. These surveys also pointed out that the areas of hemoglobin research and of coagulation research each had approximately 10 percent of their positions unfilled.

Considering the current manpower pool available, the Institute estimates a need for approximately 140 training positions in FY 75 and 240 positions in FY 76. Special emphasis is planned on formal training programs in the blood banking sciences, and in interdisciplinary approaches to thrombosis, biomaterials, and hemoglobin research.

IV. IMPLEMENTATION OF OTHER PROVISIONS OF THE ACT

IV. IMPLEMENTATION OF OTHER PROVISIONS OF THE ACT

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 significantly expanded the Institute's mandate and responsibilities. Three areas of special importance to the successful implementation of the National Program are considered in this chapter:

- National Research and Demonstration Centers
- Mechanisms of Support
- Evaluation.

NATIONAL RESEARCH AND DEMONSTRATION CENTERS

Public Law 92-423 states that the Director of the Institute may provide for the development of National Research and Demonstration Centers: up to 15 Centers for problems related to heart, blood vessel, and blood diseases; and up to 15 Centers for problems related to chronic lung diseases. The purpose of the Centers' program is to facilitate and expedite the translation of basic research findings to practical patient care in local communities across the nation. The Act specifies that this program would encompass ". . . basic and clinical research into, training in, and demonstration of, advanced diagnostic, prevention, and treatment methods . . . " for the respective diseases.

A "Program Announcement and Guidelines" for the National Centers, developed with advice from the National Heart and Lung Advisory Council, was released in August 1973. A National Research and Demonstration Center is defined as a national resource attached to a major medical complex and dedicated to working in close collaboration with the Institute to further the goals of the National Program. A Center preferably should focus on one major area--heart and blood vessel diseases, lung diseases, blood diseases, or blood resources. However, a combination of areas would be acceptable if shown to be more effective in meeting the goals of the National Program. The guidelines require

that each Center must include programs in fundamental research, clinical research and clinical application, an environment conducive to the training of young scientists, and a demonstration and education program.

Based on these guidelines, the Institute reviewed 47 applications for this program in the spring of 1974 for possible funding in FY 75. On the advice of the Council, the Institute activated only three of these Centers--one in heart and vascular diseases, one in lung diseases, and one in blood resources.

MECHANISMS OF SUPPORT

Implementation of the programs of basic and clinical research, training, education, prevention, and control that collectively make up the National Program involves the participation of a broad range of biomedical professionals. Support is provided through a variety of mechanisms. As outlined in the initial National Plan, these mechanisms range from the traditional research project grant, for the independent investigator who wishes to carry out relevant research according to a plan initiated by the investigator, to research contracts, for investigators who wish to participate in programs which are addressed to sharply targeted goals of the National Program. Between these two mechanisms are larger multidisciplinary programs, such as the Specialized Centers of Research and the National Research and Demonstration Centers. These multidisciplinary efforts, although grant-supported, combine a degree of investigator independence with mission orientation and a close working relationship with the Institute in order to integrate the efforts of one Center with the activities of other Centers and with those of the Institute.

The Institute will continue to use the fiscal mechanisms most appropriate to given activities. Investigator-initiated research must continue and be fostered as a major source of new and fresh basic scientific knowledge. At the same time, the Institute has a responsibility to society to facilitate the transfer of these scientific advances to the American health care system and to carry out programs to fill gaps of knowledge not forthcoming from grants, e.g., clinical trials, coordinated epidemiological studies, and research and development of life support devices such as oxygenators. Table 2 shows the allocation of funds between grants and contracts in FY 74. The Institute does not plan any significant change in this distribution ratio in the near future except for the addition of the National Research and Demonstration Centers. The Intramural Research noted in the table is the in-house program of basic and clinical research carried out at the National Institutes of Health.

Table 2. NHLI Resource Allocation by Major Activity

Activity	Percent of Funds FY 74*
Research Grants	55.1
Training Grants and Fellowships	5.9
Research Contracts	27.4
Intramural Research	6.9
Research Management and Program Services	4.7
TOTAL	100.0%

*Includes impounded FY 73 funds released during FY 74.

EVALUATION

The Act requires annual review and evaluation of the National Program. As mentioned in the previous annual report, approximately 300 biomedical specialists were involved in developing the original Plan for the National Program. Since that time, the activities of the National Program have been extensively reviewed and evaluated by the Institute, by the National Heart and Lung Advisory Council, by the Institute's Public Advisory and Review Groups, and by special task forces, ad hoc working groups, and consultants.

The National Heart and Lung Advisory Council plays an active role in the development, review, and evaluation of the National Program. It consists of five ex officio members and eighteen members appointed by the Secretary of the Department of Health, Education, and Welfare, including eleven leading medical or scientific authorities, two persons enrolled in residency programs, and five representatives of the general public who are leaders in fundamental or medical sciences or in public affairs. The Director of the National Heart and Lung Institute serves as chairman.

The Institute's intramural programs are evaluated by the National Heart and Lung Institute Board of Scientific Counselors. This Board consists of six members who are leaders in basic and clinical sciences related to the research activities of the Institute. The members are appointed by the Director of the National Institutes of Health, and one member is designated as chairman.

Other chartered Institute Public Advisory/Review Groups which contribute to the review and evaluation activities include:

- Arteriosclerosis and Hypertension Advisory Committee
- Blood Diseases and Resources Advisory Committee
- Cardiology Advisory Committee

- Clinical Applications and Prevention Advisory Committee
- Heart and Lung Program-Project Committee
- Lipid Metabolism Advisory Committee
- Pulmonary Diseases Advisory Committee
- Pulmonary Young Investigator Grant Committee
- Sickle Cell Disease Advisory Committee
- Clinical Trials Committee.

The activities of the National Program undergo extensive annual review and evaluation by the Institute and its advisors. As a result of this review and evaluation, changes were made in program direction (as set forth in Chapter III) during the past year. These evaluations form the basis for this annual report and updated five-year plan. Review and evaluation continues at each level of the Institute's programs and will continue to form the basis for each annual report of the Director and each annual updating of the five-year plan.

The evaluation leading to the annually updated version of the five-year plan is composed of two elements:

- Appraisal of the impact of the program activities in terms of program goals (this appraisal is summarized in Chapter III as recent progress)
- Definition of needs and opportunities determined by that appraisal (these needs and opportunities are reported in Chapter III as future challenges).

Using this information, the Institute has identified new needs and opportunities for:

- Improvements in the understanding, detection, screening, prevention, diagnosis, and treatment of disease, and the rehabilitation of patients
- New or redirected research programs using an updated state of the art
- Termination of activities not contributing to program goals
- Reorganization to meet the goals better.

The evaluation process allows the Institute to identify and promote an orderly sequence of coordinated programs. It is anticipated that, as has occurred in the first two years of the National Program, the intermediate objectives of the Program will progress from year to year toward the achievement of the ultimate goals.

As in previous years, a number of specific, targeted evaluation projects have been completed or are in the planning stages. Examples are:

- Task Force on Rehabilitation of the patient following myocardial infarction--just completed
- Evaluation of managerial effectiveness of current administrative arrangements for large-scale clinical trials--in the planning stage.

The Task Force on Rehabilitation recently reported the results of its evaluation to the Institute. It is expected that its findings will have an impact on future efforts in cardiac rehabilitation within the National Program. The Institute currently conducts several large clinical trials (described in Chapter III) which hold high priority within the National Program, and which represent a sizeable resource investment. There are real constraints in terms of medical manpower both within and without the Institute to administer and conduct such trials. There are definite limitations in terms of available subjects of suitable age, risk status, and other variables. The planned evaluation project will identify alternative management procedures and their relative cost-effectiveness. It is expected that such information will help the Institute to increase the cost-effectiveness of current and future large-scale studies within the National Program.

The results of the most recent evaluation of the National Program by the National Heart and Lung Advisory Council are presented in the second annual report of the Council.* In this report, the Council states that "It finds that substantial progress has been made and that research results are being translated rapidly into improved health care. Clearly, under the Act, much has been accomplished. Important information is being obtained . . . and it is being applied to improve medical diagnosis and treatment."

*Second Annual Report of the National Heart and Lung Advisory Council, DHEW Publication No. (NIH) 75-747, December 13, 1974.

V. RESOURCE ALLOCATION PLAN

V. RESOURCE ALLOCATION PLAN

As in last year's report, the Institute's resource projections for the National Program are based on scientific and professional judgment as to the resources required to accomplish the Program objectives within the time frame indicated. However, it is recognized that at any given time the allocation of national resources to execute the Program must be determined in relationship to other competing national needs.

FISCAL SUMMARY AND PROJECTIONS

Acting on the results of its progam review and evaluation, the Institute has reviewed and updated the fiscal projections presented in the First Annual Report of the Director in February 1974. These revised resource estimates for FY 77 to FY 81 are shown in Table 3. The projections are provided so that the planning process will stay in phase with the overall departmental planning and budgeting cycle. With the exception of the categories under Lung Diseases, the table is organized according to the same program activity categories used earlier in this report. In anticipation of FY 76 changes in program structure, the FY 77 to FY 81 estimates for Lung Diseases are presented for six categories rather than the eight discussed in this and earlier reports. In FY 76 the current program in Respiratory Assistance will be incorporated into the category of Respiratory Failure, and the program in Inhalation Diseases will be included under other relevant program areas. The table provides fiscal projections for:

- Extramural research programs in heart and blood vessel diseases, in lung diseases, and in blood diseases and blood resources, and resource allocations for each subprogram within these major disease categories

- Continued implementation of special NHLI programs authorized by Public Law 92-423: the National Research and Demonstration Centers; Prevention, Control, and Education Programs; and construction of facilities

- NHLI's Intramural Research Programs, Manpower Development Programs, and Research Management and Program Services.

Table 3. Projected Resource Allocations* for the National Heart, Blood Vessel, Lung, and Blood Program
FY 77 – FY 81
(Dollars in Millions)

Program Activities	Fiscal Years				
	1977	1978	1979	1980	1981
Extramural Research Programs					
Heart and Blood Vessel Diseases					
Arteriosclerosis	$ 58.4	$ 60.4	$ 62.4	$ 63.2	$ 61.5
Hypertension	32.2	33.3	33.8	34.5	33.0
Cerebrovascular Disease	3.9	4.0	4.1	4.1	4.1
Coronary Heart Disease	43.5	46.1	47.3	49.2	46.2
Peripheral Vascular Diseases	4.2	4.3	4.4	4.5	4.5
Arrhythmias	17.2	19.0	19.2	19.5	18.5
Heart Failure and Shock	21.3	23.6	24.9	25.9	25.1
Congenital and Rheumatic Heart Diseases	9.9	10.4	10.6	10.6	10.6
Cardiomyopathies and Infections of the Heart	3.9	5.2	6.5	7.0	7.5
Circulatory Assistance	20.9	23.9	30.9	34.8	36.2
Subtotal Heart and Blood Vessel Diseases	215.4	230.2	244.1	253.3	247.2
Lung Diseases					
Structure and Function of the Lung	11.0	11.6	12.2	11.8	11.6
Pediatric Pulmonary Diseases	7.8	8.2	9.0	8.5	8.0
Emphysema and Chronic Bronchitis	9.2	10.2	10.5	10.6	10.6
Fibrotic and Immunologic Lung Diseases	9.3	9.7	10.8	10.9	11.2
Respiratory Failure	8.2	8.8	9.2	9.2	9.2
Pulmonary Vascular Diseases	4.3	4.5	4.3	4.0	4.0
Subtotal Lung Diseases	49.8	53.0	56.0	55.0	54.6
Blood Diseases and Blood Resources					
Bleeding and Clotting Disorders	20.0	20.5	21.0	21.0	20.5
Biomaterials	3.8	4.5	4.7	5.2	5.2
Sickle Cell Disease and Other Disorders of the Red Blood Cell	18.9	19.4	19.9	20.0	20.2
Blood Resources	15.2	16.5	17.8	18.0	19.0
Subtotal Blood Diseases and Blood Resources	57.9	60.9	63.4	64.2	64.9
National Research and Demonstration Centers	25.3	48.5	55.2	56.7	58.7
Prevention, Control, and Education Programs	29.0	32.5	35.0	38.0	40.0
Construction	60.0	30.0	30.0	—	—
Manpower	40.7	47.9	48.3	48.4	48.5
Intramural Research Programs	26.0	26.0	26.0	27.0	27.0
Research Management and Program Services	28.1	29.5	31.1	30.2	30.1
TOTAL	$532.2	$558.5	$589.1	$572.8	$571.0

*This tabulation gives the primary thrust of activities, even though these activities generally involve more than one subprogram.

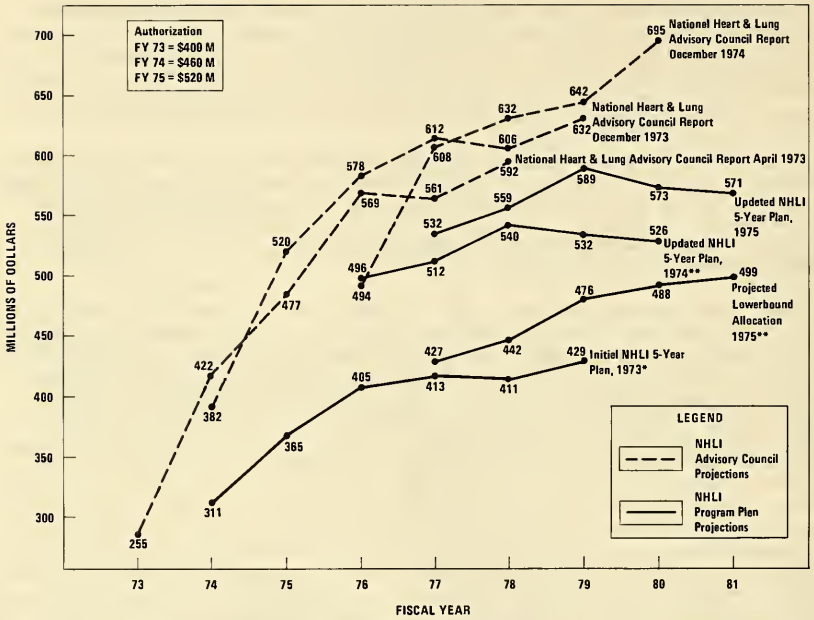
The resource allocations presented in Table 3 are consistent with the program activities projected in Chapters III and IV of this report. These allocations have been distributed in such a way as to build on past accomplishments and to anticipate future opportunities. In accordance with the legislation, at least 15 percent of the fiscal resources are projected for diseases of the lung and at least 15 percent toward the problems of blood diseases and blood resources.

The projected resource allocations give the primary thrust of activities, even though these activities generally involve more than one subprogram. Since subprograms cannot be made mutually exclusive, the allocation of a given project may be somewhat arbitrary. For example, a project involving the effects of arrhythmias in coronary heart disease upon heart failure would be categorized according to its primary thrust.

The fiscal requirements for the National Program total approximately $532 million in FY 77, an increase of $20 million over the previously recommended budget for FY 77. These requirements will increase incrementally to $589 million in FY 79; in FY 80, construction funds will not be required and the budget will decline to $573 million, and level off at $571 million in FY 81. The rationale for the resource projections for the programs in the Five-Year Plan is delineated in Chapter III of this report. The financial resources being sought for full implementation of the National Program represent a substantial increment over current resources. Except in the case of resources for Manpower, the revised resource estimates in this report represent minor modifications or changes in timing from those in the 1974 annual report. However, limitation of funds currently available, compared to those requested in the 1974 report, necessitate a prolongation of certain programs and delayed implementation or alteration of others. Figure 12 compares the projected resource allocations for the National Program as presented in the 1973, 1974, and 1975 NHLI plans. It should be emphasized that fiscal projections have not been adjusted upward for inflationary increases since preparation of the 1973 plan.

There have been no major changes in the total projected estimates for the Extramural Research Programs in Heart and Blood Vessel Diseases, Lung Diseases, and Blood Diseases and Blood Resources. However, there have been internal readjustments of resources among subprograms in each of these program areas, reflecting revised priorities, new opportunities for action, and redistribution of resources to new programs.

The Intramural Research Program is projected at the same levels as last year. Because of the delay in initiation of the National Research and Demonstration Centers, the schedule for last year's projected levels for these centers has been postponed by one year. The Prevention, Control, and Education Programs have not been initiated as visualized earlier because of limitations of funds. Hence, the resource estimates for FY 77, FY 78, and FY 79 have been revised to reflect current spending levels. For the construction funds of $60 million, $30 million, and $30 million previously projected for FY 76, FY 77, and FY 78 respectively, the schedule has been postponed by one year compared to last year's projections. The Manpower resource estimates are approximately doubled compared to those projected last year. In contrast to a year ago, the Institute now has a substantial mandate to develop research manpower. The financial needs for these programs have been documented in Chapter III of this report.



* Does not include Research Management and Program Services, estimated at 4.87% of total estimated program costs.

** Includes Research Management and Program Services.

Figure 12. Comparison of Projected Resource Allocations for the National Heart, Blood Vessel, Lung, and Blood Program (FY 73 Through FY 81)

Substantial increments in funding are necessary to fully implement the plans detailed in Chapter III. Major increased needs include the following:

- Arteriosclerosis. The understanding of the causes and treatment of arteriosclerosis must continue to grow. Large-scale clinical trials are essential to describe the natural course of the disease and to assess the effects of interventions in high risk patients through diet, drugs, and changes in lifestyle. Expanded programs are required to continue and build upon research developments in fundamental and clinical investigations. The genetic role in the genesis of arteriosclerosis must be better delineated. Experimental animal colonies with atherosclerosis must be developed for the assessment of therapeutic interventions. (For further discussion, see Arteriosclerosis under Research Programs, Chapter III.)

- Hypertension. The cause and therapy of hypertension warrant expanded investigation through the competitive review and enlargement of the program of Specialized Centers of Research on Hypertension. The Hypertension Detection and Follow-Up Program must be continued and a clinical trial of antihypertensive therapy in mild and labile hypertension must be implemented. (See Hypertension under Research Programs, Chapter III.)

- Coronary Heart Disease. An expanded scope of research on ischemic heart disease, including studies of myocardial infarction, angina pectoris, sudden cardiac death, and other manifestations of coronary heart disease must be fully implemented through the recently established Specialized Centers of Research on Ischemic Heart Disease. The medical indications and long-term effects of coronary artery surgery in the management of chronic coronary heart disease must be defined through a large-scale, multicenter clinical trial. The ongoing trial on the role of this therapy compared to medical management in acute unstable angina pectoris--which mimics acute myocardial infarction--is progressing and yielding important results. The possible efficacy of aspirin in preventing recurrent heart attacks has been investigated in feasibility trials and must be tested definitively through a large-scale, multicenter clinical trial. Methods for research on sudden cardiac death and its prevention need to be improved. Developments in the fundamental laboratories on methods of protecting heart muscle deprived of its normal blood supply are progressing to the stage where clinical investigation is warranted. Also, methods of quantifying these effects must be further refined. The needs and opportunities for rehabilitation following acute cardiac episodes have been defined and warrant implementation. (See Coronary Heart Disease under Research Programs, Chapter III.)

- Arrhythmias. The important role of arrhythmias in the cause of sudden cardiac death has been further underscored by recent evidence. Important developments in understanding the fundamental mechanisms of such arrhythmias warrant further investigation and experimental therapeutic interventions. (See Arrhythmias under Research Programs, Chapter III.)

- Heart Failure and Shock. The results of basic research on the biochemical and physiological processes of heart muscle deprived of adequate blood flow have led to promising techniques for reducing the amount of heart muscle irreversibly damaged during a heart attack. To yield definitive answers, these techniques warrant clinical investigation through large-scale, multicenter studies. (See Heart Failure and Shock under Research Programs, Chapter III.)

- Congenital and Rheumatic Heart Diseases. Comprehensive investigation on the cause, early diagnosis, and means of optimal therapy for congenital heart disease--particularly the neonatal phases--are of special importance. These warrant the establishment of Specialized Centers of Research on Congenital Heart Disease. (See Congenital and Rheumatic Heart Diseases under Research Programs, Chapter III.)

- Circulatory Assistance. The development of mechanical devices to aid the failing heart is progressing, and the need for larger-scale animal studies for preclinical validation of these devices is becoming of substantial importance. The US-USSR Agreement on Artificial Heart Research and Development must be implemented. Techniques for noninvasive detection and quantification of arteriosclerosis must be developed to expedite and improve the efficiency of clinical trials and therapy for the reduction of arteriosclerosis. These techniques will also be extremely useful for better detection and clinical assessment of arteriosclerosis. (See Circulatory Assistance under Research Programs, Chapter III.)

- Structure and Function of the Lung. Recent research advances at the cellular level hold great promise for understanding the mechanisms involved in the development of lung diseases. Individual and collaborative research efforts must be expanded in order to capitalize on these advances. (See Structure and Function of the Lung under Research Programs, Chapter III.)

- Pediatric Pulmonary Diseases. Recent important breakthroughs have occurred which make possible effective detection and therapy of hyaline membrane disease. Plans are being developed for improved management of hyaline membrane disease through programs for rapid transfer of infants with this disease to intensive care units. Programs will be initiated for improved treatment of cystic fibrosis and long-term follow-up of children with bronchiolitis. (See Pediatric Pulmonary Diseases under Research Programs, Chapter III.)

- Emphysema and Chronic Bronchitis. There is unanimous agreement that chronic respiratory disorders cannot be prevented without a knowledge of the natural history of these diseases. This requires initiation and expansion of epidemiological studies. There is an urgent need to establish, through clinical trials, the scientific bases of various therapeutic regimens which are routinely used in the treatment of chronic respiratory diseases. The rationale of these trials is two-fold. First, the efficacy of these regimens is often doubtful, yet they continue to be used because of the common belief that "they may do some good." Second, the cost of these treatments is very high (the figure of $2 billion per year has been suggested). (See Emphysema and Chronic Bronchitis under Research Programs, Chapter III.)

- National Blood Policy. The Institute will increase its efforts in support of the National Blood Policy. There is an increased need for planning, developing, and implementing targeted research in the optimal utilization of the nation's blood resources, and in reducing hepatitis. (See Blood Resources under Research Programs, Chapter III.)

- Bleeding and Clotting Disorders. Disorders of blood coagulation are a major cause of death and disability in the United States. The Institute will stimulate and expand basic and clinical research in bleeding and clotting disorders. (See Bleeding and Clotting Disorders under Research Programs, Chapter III.)

- Sickle Cell Disease. The Institute continues to coordinate the National Sickle Cell Disease Program initiated by the President in 1971. The research aspects of this program stress development of new approaches both at the fundamental and clinical levels. (See Sickle Cell Disease and Other Disorders of the Red Blood Cell under Research Programs, Chapter III.)

- National Research and Demonstration Centers. The Centers will provide an important mechanism by which the Institute can assure that the advances gained through research are translated into improved health care in the community. (See Chapter IV.)

- Prevention, Control, and Education Programs. Major program emphases discussed in Chapter III which will necessitate increased support include the following:

  - Hypertension information and education programs

  - Increased nutrition programs and risk factor detection and prevention efforts related to arteriosclerosis

  - Collaborative emergency care and rehabilitation programs related to coronary heart disease

  - Early recognition and treatment demonstration programs for cardiac and respiratory diseases of the newborn

  - Professional and public education programs concerning avoidance of noxious dust, vapors, or gases

  - Collaborative education programs aimed at smokers

  - Education programs for sickle cell disease and Cooley's anemia

  - Demonstration, screening, and education clinics for sickle cell disease

  - Education programs in hemophilia

- Hepatitis epidemiology and control programs
- Professional education regarding optimal use of blood resources.

- Construction. In its second annual report, the National Heart and Lung Advisory Council stresses the high priority on the construction of research facilities for the National Program. Construction of appropriate and adequate facilities will be important for the planned increase in program activity. The establishment of National Research and Demonstration Centers particularly requires additional funds. (See Chapter IV.)

- Manpower. An increment of resources available for manpower is dictated by the needs of the long-range research, education, and demonstration programs of the Institute as documented in Chapter III.

An alternate, lowerbound budget resource allocation plan is presented in Table 4. This plan would postpone the funding for extramural research programs by one year, as compared to the plan presented in the initial National Program in May 1973. It would defer the funding of additional centers until 1979, and limit the number of new centers to three or four. The Prevention, Control, and Education Programs would undergo only modest increases compared to the FY 76 level in the present budget. Funds for construction would be eliminated, the budget for manpower development would be reduced, and there would be modest decreases in the intramural research program. The Research Management and Program Services would be adjusted accordingly.

Table 4. Projected Lowerbound Resource Allocations for the National Heart, Blood Vessel, Lung, and Blood Program FY 77 – FY 81 (Dollars in Millions)

Program Activities	Fiscal Years				
	1977	1978	1979	1980	1981
Extramural Research Programs					
Heart and Blood Vessel Diseases	$209.2	$215.4	$230.2	$235.0	$240.0
Lung Diseases	47.2	49.8	53.0	54.1	54.6
Blood Diseases and Blood Resources	55.5	57.8	60.8	63.9	64.9
National Research and Demonstration Centers	8.0	8.0	15.0	15.0	15.0
Prevention, Control, and Education Programs	25.0	27.0	30.0	32.0	35.0
Construction	0.0	0.0	0.0	0.0	0.0
Manpower	32.0	32.0	32.5	32.5	33.0
Intramural Research Programs	25.0	26.0	26.0	26.5	26.5
Research Management and Program Services	25.3	26.2	28.2	28.9	29.5
TOTAL	$427.2	$442.2	$475.7	$487.9	$498.5

NHLI STAFF ALLOCATION PLAN

The Act requires that the Plan for the National Program include a statement which sets out the Institute's staff requirements to carry out the Program. The Institute summary of May 1973 included such a statement, noting that there were 626 authorized positions for the NHLI at that time and projecting a need for 810 positions by 1976. As of January 1, 1975, the authorized ceiling for the Institute is 671 positions. By judicious use of manpower resources, the Institute has been able to initiate activity in several areas in response to the provisions of the Act. However, it is important to emphasize that a large number of the Institute's programs require a high ratio of manpower to dollars, especially the many clinical trials and targeted programs. Examples of new activities that need additional staffing are:

- Establishment of an Office of Prevention, Control, and Education, as well as planning for prevention, control, and education programs in several areas, but particularly the programs in hypertension, which the Institute is anxious to continue and to expand
- Development of the fledgling lung programs; the entire Division of Lung Diseases currently has a full-time staff of only 21 people
- Coordination of the National Sickle Cell Disease Program
- Launching of efforts in support of the National Blood Policy with increased need to plan, develop, and implement directed research in the optimal utilization of the nation's blood resources, to reduce hepatitis, and to promote professional training and development
- Implementation of large-scale clinical trials in arteriosclerosis, hypertension, and myocardial infarction
- Establishment of the network of National Research and Demonstration Centers.

To initiate these programs, the Institute has conserved manpower in a number of ways. One was to abolish the Division of Technological Applications and divide its activities among the three categorical scientific divisions. Another way was to centralize the review function for programs supported by the contract mechanism. A third way was to consolidate some of the intramural activities.

The Institute divisions have formulated plans to implement the Action Items in the National Program. These plans, which will require additional staff to implement, are:

- The Division of Heart and Vascular Diseases will implement a full-scale multicenter clinical trial on the possible efficacy of aspirin in preventing recurrent myocardial infarction and

death (AMIS) and on the long-term efficacy and indications of coronary artery surgery (CAST); continue ongoing large-scale clinical trials such as the Multiple Risk Factor Intervention Trial (MRFIT), the lipid metabolism prevalence studies and intervention studies in high risk patients in the Lipid Research Clinics (LRC) Primary Prevention Trial, and the Hypertension Detection and Follow-Up Program (HDFP); establish Specialized Centers of Research (SCORs) on Ischemic Heart Disease; expand education, prevention, and control programs through the National High Blood Pressure Education Program (NHBPEP) and by the further development of the recently established National Research and Demonstration Center; expand research efforts on cardiovascular devices including circulatory assist pumps for aiding the failing heart; expand the development of noninvasive methods to identify, localize, and quantify heart and blood vessel diseases; establish nonhuman primate colonies with experimental arteriosclerosis for fundamental and preclinical studies; expand clinical and fundamental research on methods to minimize the amount of heart muscle damaged by heart attacks; expand research directed at preventing sudden cardiac deaths; continue implementation of the US-USSR Agreement in Health and Medical Sciences; and further stimulate and increase activity in fundamental and clinical research on all facets of heart and vascular disease.

- The Division of Lung Diseases will expand programs that apply the fundamental scientific disciplines to research on the normal and diseased lung; expand its prevention, education, and control programs; initiate and expand epidemiological studies; expand efforts to develop respiratory assist devices; and initiate clinical trials to establish the scientific basis of various therapeutic regimens in the treatment of chronic respiratory diseases. The pace of research in lung diseases, long lagging, is only now entering a phase of rapid acceleration.

- The Division of Blood Diseases and Resources will plan, develop, and implement targeted research in the optimal utilization of the nation's blood resources; expand the hepatitis program; expand prevention, control, and education programs in all blood related areas; increase efforts in professional training and development; and stimulate basic and clinical research in bleeding and clotting disorders.

- The Division of Intramural Research will require added staff for two new laboratories established during the past year (the Laboratory of Cell Biology and the Laboratory of Cellular Metabolism) and to expand the tissue culture services needed by several of the laboratories.

- The Division of Extramural Affairs, responsible for initial review of proposals in many of the above areas, will have to expand as the demand for its services increases.

To operate the National Program effectively, the NHLI needs additional staff at the middle and upper professional levels, as well as in support positions. Programs such as disease prevention, control, and education, and comprehensive centers are new to the Institute. Their review and administration requires staff with different knowledge and skills than those previously available within the Institute.

From FY 68 to the current FY 75, appropriations have increased by 93 percent, that is, nearly doubled: from $168 million in FY 68 to $324 million in FY 75. In the same period, the number of positions has increased by 13 percent, from 609 to 691. During this period several Congressional mandates for important programs have been implemented. In November 1969 (FY 70) the Institute became responsible for the lung program and the name of the Institute was changed to the National Heart and Lung Institute. As a result of the passage of the Act, the Institute received an expanded mandate in blood diseases and blood resources. Programs implemented in recent years include several major clinical trials, the enlargement of a number of targeted collaborative programs on major disease entities, specialized research programs including 42 Specialized Centers of Research and the three National Research and Demonstration Centers, as well as prevention, control, and education programs including, particularly, that for hypertension. All of these programs require a high ratio of manpower to dollar expenditure for effective management, coordination, and dollar utilization.

The Institute Summary of the National Plan of May 1973 projected staff needs of approximately 810 positions by 1976. This still remains the needed level for adequate staffing of the programs outlined in this report, despite the above mentioned efforts to conserve manpower. The level of staffing needed at the lowerbound budget projections is 760 positions.

APPENDIX

NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD ACT OF 1972

APPENDIX

NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD ACT OF 1972

Public Law 92-423
92nd Congress, S. 3323
September 19, 1972

An Act

To amend the Public Health Service Act to enlarge the authority of the National Heart and Lung Institute in order to advance the national attack against diseases of the heart and blood vessels, the lungs, and blood, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled.

National Heart, Blood Vessel, Lung, and Blood Act of 1972.

SHORT TITLE

SECTION 1. This Act may be cited as the "National Heart, Blood Vessel, Lung, and Blood Act of 1972".

FINDINGS AND DECLARATION OF PURPOSE

SEC. 2. (a) Congress finds and declares that—

(1) diseases of the heart and blood vessels collectively cause more than half of all the deaths each year in the United States and the combined effect of the disabilities and deaths from such diseases is having a major social and economic impact on the Nation;

(2) elimination of heart and blood vessel diseases as significant causes of disability and death could increase the average American's life expectancy by about eleven years and could provide for annual savings to the economy in lost wages, productivity, and costs of medical care of more than $30,000,000,000 per year;

(3) chronic lung diseases have been gaining steadily in recent years as important causes of disability and death, with emphysema alone being the fastest rising cause of death in the United States;

(4) chronic respiratory diseases affect an estimated ten million Americans, emphysema an estimated one million, chronic bronchitis an estimated four million, and asthma an estimated five million;

(5) thrombosis (the formation of blood clots in the vessels) may cause, directly or in combination with other problems, many deaths and disabilities from heart disease and stroke which can now be prevented; 86 STAT. 679

(6) blood and blood products are essential human resources 86 STAT. 680 whose value in saving life and promoting health cannot be assessed in terms of dollars;

(7) the provision of prompt and effective emergency medical services utilizing to the fullest extent possible advances in transportation and communications and other electronic systems and specially trained professional and paraprofessional health care personnel can reduce substantially the number of fatalities and severe disabilities due to critical illnesses in connection with heart, blood vessel, lung, and blood diseases; and

(8) the greatest potential for advancement against heart, blood vessel, lung, and blood diseases lies in the National Heart and Lung Institute, but advancement against such diseases depends not only on the research programs of that Institute but also on the research programs of other research institutes of the National Institutes of Health.

(b) It is the purpose of this Act to enlarge the authority of the National Heart and Lung Institute in order to advance the national attack upon heart, blood vessel, lung, and blood diseases.

83-749 O (260)

HEART, BLOOD VESSEL, LUNG, AND BLOOD DISEASE PROGRAMS

62 Stat. 464. 42 USC 287-287c.

SEC. 3. Part B of title IV of the Public Health Service Act is amended (1) by redesignating section 413 as section 419A. (2) by redesignating section 414 as section 418, and (3) by adding after section 412 the following new sections:

"NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD DISEASE PROGRAM

"SEC. 413. (a) The Director of the Institute, with the advice of the Council, shall develop a plan for a National Heart, Blood Vessel, Lung, and Blood Disease Program (hereafter in this part referred to as the 'Program') to expand, intensify, and coordinate the activities of the Institute respecting heart, blood vessel, lung, and blood diseases (including its activities under section 412) and shall carry out the Program in accordance with such plan. The Program shall be coordinated with the other research institutes of the National Institutes of Health to the extent that they have responsibilities respecting such diseases and shall provide for—

NIH, coordination provisions.

"(1) investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases;

"(2) studies and research into the basic biological processes and mechanisms involved in the underlying normal and abnormal heart, blood vessel, lung, and blood phenomena;

"(3) research into the development, trial, and evaluation of techniques, drugs, and devices (including computers) used in, and approaches to, the diagnosis, treatment (including emergency medical service), and prevention of heart, blood vessel, lung, and blood diseases and the rehabilitation of patients suffering from such diseases;

86 STAT. 680

86 STAT. 681

"(4) establishment of programs that will focus and apply scientific and technological efforts involving biological, physical, and engineering sciences to all facets of heart, blood vessel, lung, and blood diseases with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improve instrumentation for detection, diagnosis, and treatment of those diseases;

"(5) establishment of programs for the conduct and direction of field studies, large-scale testing and evaluation, and demonstration of preventive, diagnostic, therapeutic, and rehabilitative approaches to, and emergency medical services for, such diseases;

"(6) studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country, including the collection, preservation, fractionalization, and distribution of it and its products;

"(7) the education and training of scientists, clinicians, and educators, in fields and specialties (including computer sciences) requisite to the conduct of programs respecting heart, blood vessel, lung, and blood diseases;

"(8) public and professional education relating to all aspects of such diseases and the use of blood and blood products and the management of blood resources:

"(9) establishment of programs for study and research into heart, blood vessel, lung, and blood diseases of children (including cystic fibrosis, hyaline membrane, and hemolytic and hemophilic

diseases) and for the development and demonstration of diagnostic, treatment, and preventive approaches to these diseases; and

"(10) establishment of programs for study, research, development, demonstrations and evaluation of emergency medical services for people who become critically ill in connection with heart, blood vessel, lung, or blood diseases, which programs shall include programs for (A) the training of paraprofessionals in (i) emergency treatment procedures, and (ii) utilization and operation of emergency medical equipment, (B) the development and operation of (i) mobile critical care units (including helicopters and other airborne units where appropriate), (ii) radio, telecommunications, and other means of communications, and (iii) electronic monitoring systems, and (C) the coordination with other community services and agencies in the joint use of all forms of emergency vehicles, communications systems, and other appropriate services.

The Program shall give special emphasis to the continued development in the Institute of programs relating to atherosclerosis, hypertension, thrombosis, and congenital abnormalities of the blood vessels as causes of stroke, and to effective coordination of such programs with related stroke programs in the National Institute of Neurological Diseases and Stroke. National Institute of Neurological Diseases and Stroke, coordination.

"(b)(1) The plan required by subsection (a) of this section shall (A) be developed within one hundred and eighty days after the effective date of this section, (B) be transmitted to the Congress, and (C) set out the Institute's staff requirements to carry out the Program and recommendations for appropriations for the Program. Plan development; transmittal to Congress. 86 STAT. 681 86 STAT. 682

"(2) The Director of the Institute shall, as soon as practicable after the end of each calendar year, prepare in consultation with the Council and submit to the President for transmittal to the Congress a report on the activities, progress, and accomplishments under the Program during the preceding calendar year and a plan for the Program during the next five years. Report to President, transmittal to Congress.

"(c) In carrying out the Program, the Director of the Institute, under policies established by the Director of the National Institutes of Health and after consultation with the Council and without regard to any other provision of this Act, may— Director, functions.

"(1) if authorized by the Council, obtain (in accordance with section 3109 of title 5, United States Code, but without regard to the limitation in such section on the number of days or the period of such service) the services of not more than fifty experts or consultants who have scientific or professional qualifications; 80 Stat. 416.

"(2) acquire, construct, improve, repair, operate, and maintain heart, blood vessel, lung, and blood disease laboratory, research, training, and other necessary facilities and equipment, and related accommodations as may be necessary, and such other real or personal property (including patents) as the Director deems necessary; and acquire, without regard to the Act of March 3, 1877 (40 U.S.C. 34), by lease or otherwise, through the Administrator of General Services, buildings or parts of buildings in the District of Columbia or communities located adjacent to the District of Columbia for the use of the Institute for a period not to exceed ten years; and 19 Stat. 370.

"(3) enter into such contracts, leases, cooperative agreements, or other transactions, without regard to sections 3648 and 3709 of the Revised Statutes of the United States (31 U.S.C. 529, 41 U.S.C. 5), as may be necessary in the conduct of his functions, with any public agency, or with any person, firm, association, corporation, or educational institution.

Assistant Director for Health Information Programs. Cardiovascular and pulmonary diseases, information.

"(d) There shall be in the Institute an Assistant Director for Health Information Programs who shall be appointed by the Director of the Institute. The Director of the Institute, acting through the Assistant Director for Health Information Programs, shall conduct a program to provide the public and the health professions with health information with regard to cardiovascular and pulmonary diseases. In the conduct of such program, special emphasis shall be placed upon dissemination of information regarding diet, exercise, stress, hypertension, cigarette smoking, weight control, and other factors affecting the prevention of arteriosclerosis and other cardiovascular diseases and of pulmonary diseases.

"HEART, BLOOD VESSEL, LUNG, AND BLOOD DISEASE PREVENTION AND CONTROL PROGRAMS

"SEC. 414. (a) The Director of the Institute, under policies established by the Director of the National Institutes of Health and after consultation with the Council, shall establish programs as necessary for cooperation with other Federal Health agencies, State, local, and regional public health agencies, and nonprofit private health agencies in the diagnosis, prevention, and treatment (including the provision of emergency medical services) of heart, blood vessel, lung, and blood diseases, appropriately emphasizing the prevention, diagnosis, and treatment of such diseases of children.

86 STAT. 682
86 STAT. 683

Appropriations.

"(b) There is authorized to be appropriated to carry out this section $25,000,000 for the fiscal year ending June 30, 1973, $35,000,000 for the fiscal year ending June 30, 1974, and $45,000,000 for the fiscal year ending June 30, 1975.

"NATIONAL RESEARCH AND DEMONSTRATION CENTERS FOR HEART, BLOOD VESSEL, LUNG, AND BLOOD DISEASES

"SEC. 415. (a) (1) The Director of the Institute may provide for the development of—

"(A) fifteen new centers for basic and clinical research into, training in, and demonstration of, advanced diagnostic, prevention, and treatment methods (including methods of providing emergency medical services) for heart, blood vessel, and blood diseases; and

"(B) fifteen new centers for basic and clinical research into, training in, and demonstration of, advanced diagnostic, prevention, and treatment methods (including methods of providing emergency medical services) for chronic lung diseases (including bronchitis, emphysema, asthma, cystic fibrosis, and other lung diseases of children).

"(2) The centers developed under paragraph (1)(A) shall, in addition to being utilized for research, training, and demonstrations, be utilized for the following prevention programs for cardiovascular diseases:

"(A) Programs to develop improved methods of detecting individuals with a high risk of developing cardiovascular disease.

"(B) Programs to develop improved methods of intervention against those factors which cause individuals to have a high risk of developing such disease.

"(C) Programs to develop health professions and allied health professions personnel highly skilled in the prevention of such disease.

"(D) Programs to develop improved methods of providing emergency medical services for persons with such disease.

"(3) Centers developed under this subsection may be supported under subsection (b) or under any other applicable provision of law. The research, training, and demonstration activities carried out through any such center may relate to any one or more of the diseases referred to in paragraph (1) of this subsection.

"(b) The Director of the Institute, under policies established by the Director of the National Institutes of Health and after consultation with the Council, may enter into cooperative agreements with public or nonprofit private agencies or institutions to pay all or part of the cost of planning, establishing, or strengthening, and providing basic operating support for, existing or new centers (including centers established under subsection (a)) for basic or clinical research into, training in, and demonstration of, advanced diagnostic, prevention, and treatment methods for heart, blood vessel, lung, or blood diseases. Funds paid to centers under cooperative agreements under this subsection may be used for— Public or nonprofit agencies, cooperative agreements. Use of funds.

"(1) construction, notwithstanding section 405, 58 Stat. 708.

"(2) staffing and other basic operating costs, including such patient care costs as are required for research, 42 USC 285. 86 STAT. 683

"(3) training, including training for allied health professions personnel, and 86 STAT. 684

"(4) demonstration purposes.

The aggregate of payments (other than payments for construction) made to any center under such an agreement may not exceed $5,000,000 in any year. Support of a center under this subsection may be for a period of not to exceed five years and may be extended by the Director of the Institute for additional periods of not more than five years each, after review of the operations of such center by an appropriate scientific review group established by the Director. As used in this section, the term 'construction' does not include the acquisition of land. Limitations. "Construction."

"INTERAGENCY TECHNICAL COMMITTEE

"SEC. 416. (a) The Secretary shall establish an Interagency Technical Committee on Heart, Blood Vessel, Lung and Blood Diseases and Blood Resources which shall be responsible for coordinating those aspects of all Federal health programs and activities relating to heart, blood vessel, lung, and blood diseases and to blood resources to assure the adequacy and technical soundness of such programs and activities and to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities. Establishment.

"(b) The Director of the Institute shall serve as Chairman of the Committee and the Committee shall include representation from all Federal departments and agencies whose programs involve health functions or responsibilities as determined by the Secretary.

"NATIONAL HEART AND LUNG ADVISORY COUNCIL

"SEC. 417. (a) There is established in the Institute a National Heart and Lung Advisory Council to be composed of twenty-three members as follows: Establishment; membership.

"(1) The Secretary, the Director of the National Institutes of Health, the Director of the Office of Science and Technology, and the chief medical officer of the Veterans' Administration (or their designees), and a medical officer designated by the Secretary of Defense, shall be ex officio members of the Council.

"(2) Eighteen members appointed by the Secretary.

Eleven of the appointed members shall be selected from among the leading medical or scientific authorities who are skilled in the sciences

86 STAT. 687

(2) by striking out "Surgeon General" each place it occurs (except paragraph (f)) and inserting in lieu thereof "Secretary";

(3) by striking out "heart" each place it occurs and inserting in lieu thereof "heart, blood vessel, lung, and blood";

(4) by striking out "Surgeon General" in paragraph (f) and inserting in lieu thereof "Secretary, the Director of the National Institutes of Health, and the Director of the National Heart and Lung Institute"; and

(5) by redesignating paragraphs (a), (b), (c), (d), (e), and (f) as paragraphs (1), (2), (3), (4), (5), and (6), respectively.

(d) Section 419A of such Act (as so redesignated by section 3 of this Act) is amended—

(1) in subsection (a), by (A) striking out "Surgeon General" and inserting in lieu thereof "Secretary", and (B) striking out "heart" and inserting in lieu thereof "heart, blood vessel, lung, and blood"; and

(2) in subsection (b), by (A) striking out "The Surgeon General shall recommend to the Secretary acceptance of conditional gifts, pursuant to section 501," and inserting in lieu thereof "The Secretary may, in accordance with section 501, accept conditional gifts", and (B) striking out "heart" and inserting in lieu thereof "heart, blood vessel, lung, and blood".

58 Stat. 709.
42 USC 219.

(e) The heading for part B of such Act is amended to read as follows:

"PART B—NATIONAL HEART AND LUNG INSTITUTE".

CONFORMING AMENDMENTS TO OTHER PROVISIONS OF THE PUBLIC HEALTH SERVICE ACT

SEC. 7. (a) Section 217 of such Act is amended—

64 Stat. 446.
42 USC 218.

(1) by striking out "the National Advisory Heart Council," each place it occurs in subsection (a);

(2) by striking out "heart diseases," in subsection (a) and by striking out "heart," in subsection (b).

58 Stat. 692;
62 Stat. 601;
79 Stat. 448.
42 USC 241.

(b) Sections 301(d) and 301(i) of such Act are each amended by striking out "National Advisory Heart Council" and inserting in lieu thereof "National Heart and Lung Advisory Council".

REPORT TO CONGRESS

Review.

SEC. 8. The Secretary of Health, Education, and Welfare shall carry out a review of all administrative processes under which the National Heart, Blood Vessel, Lung, and Blood Disease Program, established under part B of title IV of the Public Health Service Act, will operate, including the processes of advisory council and peer group reviews, in order to assure the most expeditious accomplishment of the objectives of the Program. Within one year of the date of enactment of this Act, the Secretary shall submit a report to the Congress of the findings of such review and the actions taken to facilitate the conduct of the Program, together with recommendations for any needed legislative changes.

Ante, p. 680.

EFFECTIVE DATE

SEC. 9. This Act and the amendments made by this Act shall take effect sixty days after the date of enactment of this Act or on such prior date after the date of enactment of this Act as the President shall prescribe and publish in the Federal Register. Publication in Federal Register.

Approved September 19, 1972.

LEGISLATIVE HISTORY:

HOUSE REPORTS: No. 92-1108 accompanying H.R. 15081 (Comm. on Interstate and Foreign Commerce) and No. 92-1349 (Comm. of Conference).
SENATE REPORTS: No. 92-733 (Comm. on Labor and Public Welfare) and No. 92-1068 (Comm. of Conference).
CONGRESSIONAL RECORD, Vol. 118 (1972):
Apr. 7, considered and passed Senate.
July 18, considered and passed House, amended, in lieu of H.R. 15081.
Aug. 18, House agreed to conference report.
Sept. 6, Senate agreed to conference report.
WEEKLY COMPILATION OF PRESIDENTIAL DOCUMENTS, Vol. 8, No. 39:
Sept. 20, Presidential statement.

DATE DUE

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